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CARCINOMA OF THE CERVIX ASSOCIATED WITH PREGNANCY

A Study of the Radiumhemmet s Series of Invasive Carcinoma During the Period 1932—56

BY

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Introduction

Carcinoma of the cervix may occur at all ages and in pregnant women The incidence of carcinoma of the cervix during preg nancy varies considerably from publication to publication The number of obstetrical cases having carcinoma of the cervix has been found to be 014 per cent (Hayden 1956) 023 per cent (Jensen 1944) and 05 per cent (Hirst, 1951) The number of cases of carcinoma of the cervix associated with pregnancy has been quoted as 55 per cent (Truelsen 1949), 1 54 per cent (Johnson, 1950), 2 4 per cent (Sadugor, 1949) and 3 0 per cent (Halzaepfel 1955) Among the reasons for variations from series to series in these figures are 1) differences in the numbers of cases which are diagnosed during the antepartum period 2) differences in the duration of post partum studies, 3) the inclusion of carcinoma *in situ* in some studies 4) small and statistically inaccurate series and 5) differences in the birth rate in the populations studied

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In the study at the Mayo Clinic in 1944, 30 per cent of 20 cases of carcinoma of the cervix associated with pregnancy were clinically healed after five years These cases had been treated with radiotherapy, surgery and a combination of both methods The largest study at one institution was made at the Roswell Park Memorial Hospital in 1949 Of the 124 cases treated between 1917 and 1949, 36 were pregnant and 88 post partum when they were admitted for therapy Seventeen had received therapy prior to arrival, consisting primarily of surgery, the five year survival rate of these 17 cases was 5 9 per cent There was a five year survival rate of 26 9 per cent among the 78 patients who were admitted without previous therapy and who were treated with radiotherapy at that hospital 1933–42 This latter figure was compared with a five year survival rate of 27 5 per cent for all of the 3,251 cases of carcinoma of the cervix treated at that hospital during the same period Unfortunately no differentiation was made between the results of those treated during and following pregnancy The recommendation from that institution was radiotherapy in the period prior to the viability of the infant and, for those patients with a viable infant, Cæsarean section followed in ten days to two weeks by irradiation therapy Patients in the early stages of pregnancy aborted spontaneously, usually by the end of the third week following external irradiation

Materials and Methods

Since the problem of diagnosis and treatment of carcinoma *in situ* is quite different from that of invasive carcinoma, only invasive carcinoma of the cervix is discussed in this report The emphasis is on the therapeutic aspects of carcinoma of the cervix associated with pregnancy and this is discussed in regard to the general experience of therapy at the Radiumhemmet and to various methods of treatment used at other institutions A survey of the literature has been made but in this paper reference is made to only some of the articles published Since it is sometimes difficult to obtain references from the literature, we believe that a complete bibliography is of value and therefore include a full list of references used in this survey

A total number of 7,192 cases of carcinoma of the cervix were treated at the Radiumhemmet during the 24 years 1932 to 1956 Among these were 239 cases which were associated with pregnancy, an incidence of 3 3 per cent Eighty two, or 1 1 per cent, were diagnosed during pregnancy The 239 patients had an average age of 34 1 years, an average gravidity of 3 6, an average parity of 3 1, and an average period of bleeding or foul smelling discharge of 4 5 months Eighty-eight per cent had a history of bleeding and an additional 8 3 per cent had a history of foul smelling discharge Histologically 7 cases were adenocarcinomas, 7 were mucin producing squamous cell carcinomas similar to adenocarcinoma, and 225 cases were epidermoid squamous cell carcinomas

The cases are divided into the following 4 groups according to the time of diagnosis

Group 1 Carcinoma of the cervix diagnosed during the first and second trimesters of pregnancy (67 cases)
Group 2 Carcinoma of the cervix diagnosed during the third trimester of pregnancy (15 cases)
Group 3 Carcinoma of the cervix diagnosed during the 6 months following pregnancy (79 cases)
Group 4 Carcinoma of the cervix diagnosed within 7 to 12 months following pregnancy (78 cases)

Each group is discussed separately

Group 1 Carcinoma of the Cervix Diagnosed During the First and Second Trimesters of Pregnancy

Review of the Literature

Corscaden (1956) discussed the various methods of therapy for carcinoma of the cervix occurring during pregnancy In general there are four methods which can be applied three of which are chiefly important during early pregnancy The four methods are *1)* the induction of abortion through rœntgen therapy and following the abortion the administration of radium and additional rœntgen therapy 2) dilation and curettage followed by irradiation therapy, 3) radical Wertheim hysterectomy and 4)

hysterotomy or Cæsarean section followed by (a) intra cavitary radium and external rœntgen therapy, (b) Porro supravaginal hysterectomy followed by irradiation therapy, (c) radical Wertheim hysterectomy, or (d) radium and rœntgen therapy followed by Wertheim hysterectomy

There are many reports on cases treated in the first two trimesters As a rule the authors present only a small number of cases which do not permit any conclusions to be drawn as far as the method of treatment is concerned Heyman (1947) reported 9 cases treated with surgery and post operative irradiation Only one of the 9 cases survived five years A similar experience was noted by Maier (1951) and also by Hudgins (1952) Schubert (1960), on the other hand, reported 9 cases diagnosed during the first two trimesters and no less than 8 have survived *for five years Intra cavitary radium and external irradiation was* applied in 7 of these cases following a supravaginal hysterectomy The other two were treated by Wertheim hysterectomy and rœntgen therapy Four of the cases were in stage I, 3 in stage II and 2 in stage III

Jones (1944) reported 7 cases of which 5 were in stage I and 2 in stage II Radium therapy in the range of 1,614 to 3,900 mgm hrs was given to the cervix A Cæsarean section was carried out from one to five months after the radium therapy Additional irradiation therapy was given following the Cæsarean section Five of the 7 patients were living and symptom free at five years but 2 of the children had micro cephaly

Analysis of the Material at the Radiumhemmet, First and Second Trimesters of Pregnancy

There were 67 cases diagnosed during the first two trimesters of pregnancy They had an average duration of bleeding or foul smelling discharge of 4 1 months These 67 cases were staged in accordance with the League of Nations classification as follows stage I 32, stage II 28, stage III 3 and stage IV 4 cases The configuration of the tumour lesions was a crater in 9, a cauliflower growth in 11 and a disc in 47 cases

Therapy

The method of therapy at the Radiumhemmet for carcinoma of the cervix associated with pregnancy has remained basicly the same since 1932 The current method of therapy administered to patients with carcinoma of the cervix complicating the first two trimesters of pregnancy is combined intra cavitary radium and external radiotherapy Initially the patient undergoes a careful examination including cystoscopy, urography, and sometimes phle bography

As a rule irradiation is begun with intra cavitary radium in the endocervix and the vagina Several types of intrauterine and intra vaginal applicators are used The filter is equivalent to two or three mm of lead A long intrauterine applicator is introduced into the endocervix The amount of radium (element) contained in the typical intrauterine applicator varies from 53 to 74 mgm It is designed to give a uniform dosage in gamma r at a distance of 20 mm or more from the centre of the applicator

One or more flat or curved boxes or two to three cylinders are used in the vagina for the same length of time The intra vaginal applicator is made of lead or monel The amount of radium varies from 60 to 100 mgm in the typical applicators These are arranged and constructed so as to cover the vaginal surface of the tumour, to press the lateral fornices against the lateral pelvic walls and to spread out the radium over a large area The radium tubes are usually placed in the lateral parts of the applicators These applicators are held in position by a tampon which also serves to increase the distance of the radium from the rectum The irradiation time is 25 to 28 hours for each of two typical radium treatments The interval between the radium ap plications is about three weeks in uncomplicated cases

The first intra cavitary radium treatment is immediatelv fol lowed by external irradiation from two to four anterior portals depending on the size of the uterus and the stage of pregnancy As a rule a dose of 400 skin r is given daily to one portal but in the late second trimester two fields may receive roentgen therapy every day A dose of 1,600 to 2,400 r is given to each field with conventional roentgen therapy The half value layer of the radia tion is 0 8 mm of copper

Three to four weeks following the first radium therapy the patient is reexamined and the application then depends on the situation at that time If abortion has already taken place, the patient receives a radium application according to the current Stockholm technique as though she had not been pregnant If abortion has not yet occurred, the radium application is repeated in the manner described above At a later date, usually following an interval of two to four weeks, rœntgen or cobalt therapy is given to the parametrium from two posterior fields

Therapy as Applied in these Cases

A curettage for incomplete abortion was performed in one case simultaneously with the clinical diagnosis of carcinoma of the cervix and a cervical biopsy and surgical abortion were performed in seven other cases Among the seven latter cases, four had a dilatation and curettage because of bleeding Two of the remaining three cases had a vaginal hysterotomy and the other one had an abdominal hysterotomy

Of the 67 patients in the first or second trimesters 59 were pregnant when radiotherapy was begun The average period between the onset of radiotherapy and abortion was 29 days and varied from 3 to 99 days An attempt was made to obtain spontaneous abortion This occurred in 58 cases but 6 of these subsequently required a curettage for incomplete abortion In the remaining case a dilatation and curettage was performed prior to abortion in order to control bleeding

Two of the 67 patients had definitive surgery in addition to the radiotherapy as part of the originally planned therapy One case, a patient with a stage III carcinoma and a four month gestation had a radical hysterectomy immediately following the completion of the radiotherapy Carcinoma was found on the pelvic wall at the time of surgery and she died from carcinoma of the cervix Another case, a stage I, had a bilateral extraperitoneal lymphadenectomy at the time of the radium therapy She has been free from evidence of disease for 11 years

Complications Following Primary Therapy

No serious complications occurred in connection with the abortion Several patients had an increased temperature but this was of short duration No cervical lacerations occurred at the time of abortion and only three patients required curettage at the time of abortion to control bleeding

An elevation of the temperature was seen in several cases during the radium therapy but in only one case was it necessary to interrupt the therapy because of sepsis Salpingitis occurred in one case after the first radium treatment A bilateral salpingo ophorectomy was performed and the second course of radium therapy progressed uneventfully

Slight late bladder or rectal reactions occurred in three patients but in no case did any injury occur

Remarks

As described above, the principle at the Radiumhemmet has been to treat the patient for the carcinoma of the cervix during the first two trimesters without regard to the pregnancy The pregnancy may be interrupted by the irradiation and spontaneous abortion results Because of the circumstances it is not possible to apply the radium with a satisfactory dose distribution in each individual case Therefore several cases subsequently received additional therapy several weeks after the abortion, that is at a time when the uterus had involuted

During the first six months following the onset of therapy additional palliative or definitive therapy was given in 10 patients who failed to survive five years As the principle form of secondary therapy, 6 cases received additional radiotherapy, one had intra parametrial colloidal gold and 3 had surgical therapy In 7 other patients who survived five years or more additional palliative or definitive therapy was given during the first six months following the onset of therapy Six of these received electro coagulation therapy and one received intra parametrial colloidal gold

In the period six months to five years following the onset of therapy there were 9 cases who developed recurrences and failed

to survive five years Five cases received irradiation, as the principle form of definitive or palliative therapy, one was treated with electrocoagulation and a radical *Wertheim* hysterectomy was performed in one case Two patients received no additional therapy Among the five year survivals, three cases were treated for clinical recurrences six months after the diagnosis The therapy consisted of local electro coagulation

Results

Among the 67 patients in this group, 30 cases healed after primary therapy Twenty-seven cases received additional therapy because of clinical recurrence or radioresistance of the tumour Ten of the latter patients survived for five years or more

There were 40 patients who survived five or more years, a rate of 59 7 per cent The survival rates according to stages were stage I 23 of 32 cases or 71 8 per cent, stage II 16 of 28 cases or 57 1 per cent, stage III one of 3 cases or 33 3 per cent and stage IV none of 4 cases or 0 per cent

Group 2 Carcinoma of the Cervix Diagnosed During the third Trimester of Pregnancy

Review of the Literature

Many authors have reported occasional cases of carcinoma of the cervix in the third trimester of pregnancy The treatment has varied from primary surgery to primary irradiation following Cæsarean section or Porro section In general the results have been poor Maino (1944) had a series of 11 cases in which various kinds of therapy were tried Only two of these 11 patients survived five years Petersen s (1947) three case reports are of interest One patient who was in the second trimester had a pea size carcinomatous lesion on the cervix She was treated with intravaginal radium and delivered spontaneously four months later At the time of reporting she had survived for eight years Another case who was in the early third trimester of pregnancy had a carcinomatous lesion limited to the cervix The patient was

Table 1 *Carcinoma of the Cervix Treated During and Following Pregnancy at the Radiumhemmet 1932–56*
A Comparison of the Five Year Survivals According to the Different Groups Studied

Group and Number of Cases Treated	Stage I No.	Stage I Per cent	Stage II No	Stage II Per cent	Stage III No	Stage III Per cent	Stage IV No	Stage IV Per cent
Group 1 67 cases	23	71 8 %	16	57 1 %	1	33 3 %	0	0
Group 2 15 cases	3	100 0 %	1	16 6 %	0	0 %	0	0
Group 3 79 cases	11	91 6 %	21	48 8 %	4	26 6 %	0	0
Group 4 78 cases	5	62 5 %	26	49 0 %	1	8 3 %	0	0
Total 239 cases	42	76 4 %	64	49 2 %	6	17 1 %	0	0

No cases have been lost during follow up

Group 1 Carcinoma of the cervix diagnosed during the first and second trimesters of pregnancy *Group 2* Carcinoma of the cervix diagnosed during the third trimester of pregnancy *Group 3* Carcinoma of the cervix diagnosed during the six months following pregnancy *Group 4* Carcinoma of the cervix diagnosed during the period 7 to 12 months following pregnancy

treated with vaginal radium and spontaneous delivery occurred two months later The patient was alive and well after five years and has had another child since therapy A third case in the third trimester of pregnancy had a slightly more advanced tumour which was treated with intravaginal radium Two months later she delivered spontaneously and was treated with additional radiotherapy but she died of carcinoma of the cervix

Analysis of the Material at the Radiumhemmet Third Trimester of Pregnancy

There were 15 patients in whom the diagnosis of carcinoma was made during the third trimester of pregnancy These patients had an average duration of symptoms of 3 9 months They were staged in accordance with the League of Nations classification as follows stage I 3 stage II 6, stage III 5 and stage IV 1 case The gross

configuration of the tumour was a crater in three, a cauliflower in four and a disc in 8 cases

Therapy

The treatment varied in the 15 cases Even though the gesta tion was in the seventh month, primary irradiation in accordance with the therapy applied in the first two trimesters was given in 3 cases of stage I lesions Delivery occurred spontaneously in 2 cases on the seventh and 45th day after the onset of therapy A Cæsarean section was performed in the third case seven days after the first radium application The child was born alive but did not survive No complications occurred in any of these cases The patients are living and symptom free 22, 19 and 6 years after the initial diagnosis

One additional case was permitted to deliver vaginally This was a 29 year old woman with a full term pregnancy in whom there were no fœtal heart sounds heard on admission She received intravaginal and endocervical radium therapy After 30 hours of labour she delivered a 3,300 gram macerated fœtus A retained placenta necessitated manual removal She died of sepsis 18 days following admission

Among 9 patients in whom the diagnosis of carcinoma of the cervix was made coincidentally with a full term pregnancy, an abdominal Cæsarean section was performed in 6 and a Porro section was performed in 3 cases Four cases were classified as stage II, four as stage III and one as stage IV The surgical treat ment was performed at other hospitals from which the patients were transferred to the Radiumhemmet for irradiation therapy In these cases the first radium was inserted into the vagina or into the endocervix and vagina on the 1st, 3 rd 5th, 10th, 14th, 27th, 33rd and 51st day following surgery In the last mentioned case the radiotherapy was delayed because of a pulmonary embolus which was being treated at another hospital

Three of the 9 patients developed sepsis during therapy and thus necessitated the interruption of treatment Eight of the cases died between 3 1/2 and 18 months after the initial diagnosis One patient, a stage II case, has survived for 12 years

As a sequel to the extremely poor results obtained in these 9 cases with only one five year survival, and the rather satisfactory results in those treated by primary irradiation, we have tried primary intravaginal radiation therapy in two cases in which there was a viable fœtus We are well aware of the risks to the fœtus by an application of intravaginal radium and therefore we have made an effort to increase as much as possible the distance from the radium to the fœtus This was accomplished by the conversion of the fœtus to a breech presentation and by keeping the patient in the Trendelenberg position during the therapy This approach which had been described previously by Petersen (1947) and Mikulicz-Radecki (1941) was tried in two cases and they are discussed in detail

The first case was a 28 year old gravida six para five with a stage II carcinoma in the eighth month of gestation She received 243 mg of radium contracervically for 12½ hours The therapy was repeated 24 days later and she then received 102 mg for 20 hours Thirty five days from the time of the first radium therapy the patient underwent a Cæsarean section salpingectomy and bilateral pelvic lymphadenectomy The child appearad normal at birth Five days following surgery 350 mg of radium were placed in the uterus for 12 hours This was followed by external irradiation therapy 1 600 skin r to four fields A vaginal recurrence three months after the original diagnosis was treated by electro-coagulation Seven months from the time of the original diagnosis a total Brunschwig exenteration was performed because of a local recurrence She survived a total of eight months

The second case was a 32 year old patient with a stage II lesion She had 100 mg of radium placed in the vagina for 16 hours and two days later a Cæsarean section was performed The child was well at birth The day following surgery 180 mg of radium were placed in the uterus for 20 hours and three weeks later she recived intrauterine and intravaginal radium followed by rœntgen. Three months following the initial therapy colloidal gold was injected into the parametrium because of continued tumour growth and this was repeated at 12 months She survived 25 months

There were no delayed complications from the primary therapy

Results

All three patients who were in the seventh month of gestation and who were treated with primary radiotherapy (followed by Cæsarean section in one case) survived for at least 5 years The patient with a term pregnancy who received primary radiotherapy

died from complications of the therapy There was only one five year survivor among the nine who were treated by Cæsarean section or Porro section followed by radiotherapy Neither of the two cases which received radiation therapy to the cervix followed by Cæsarean section survived five years

There were 4 patients (26 6 per cent) out of the 15 who survived five years or more They included all three of the stage I lesions (100 per cent) and one of the six stage II lesions (16 6 per cent) The 5 cases in stage III and the one case in stage IV failed to survive five years

Group 3 Carcinoma of the Cervix Diagnosed During the Six Months Following Pregnancy

Review of the Literature

Many authors have given reports on selected cases of carcinoma of the cervix following pregnancy which were treated either by surgery or by radiotherapy Truelsen (1949) collected a series of 35 cases treated by irradiation Only seven patients were living and symptom free after five years McDuff (1956) presented four cases, three in stage II, and one in stage III Two patients were living and symptom free at 2 and 15 years when reported Johnson (1950) reported five cases, one of which is of interest as the carcinoma occurred coincidentally with an ectopic pregnancy The cancer was allotted to stage I A supracervical hysterectomy and bilateral oophorectomy were performed and this was followed by the vaginal application of radium The patient is alive after 16 years Two other patients with stage II carcinomas were treated by irradiation and surgery and were free from evidence of disease for at least five years Two patients with a more advanced lesion died from the cancer

Analysis of the Material at the Radiumhemmet, Diagnosed within Six Months Following Pregnancy

There were 79 cases diagnosed during the six months following pregnancy Sixty of these were post partum and 19 were post

Table II *Carcinoma of the Cervix Treated at the Radiumhemmet 1932–56*
A Comparison of the Results of All Cases Treated with Those Treated During and Following Pregnancy

Stage	All cases of Carcinoma of the Cervix		Cases of Carcinoma of the Cervix During and Following Pregnancy	
	No of Cases	Per cent Five Year Survivals	No of Cases	Per cent Five Year Survivals
I	964	79 5 %	55	76 4 %
II	3768	52 2 %	130	49 2 %
III	1843	26 8 %	35	17 1 %
IV	617	7 8 %	19	0 %
Total	7192	45 5 %	239	46 9 %

No cases have been lost during follow up

abortion They had an average duration of bleeding or of foul smelling discharge of 4 4 months They were staged in accordance with the League of Nations classification as follows stage I 12 cases, stage II 43 cases, stage III 15 cases and stage IV 9 cases Among the 79 cases the gross configuration of the tumour lesion was a cauliflower in 22 cases a crater in 25 and a disc in 32 cases

Therapy

The therapy administered during the post partum period is a combined intra-cavitary radium and rœntgen therapy in accordance with the Stockholm technique No radium is inserted into the lower 1 1/2 to 2 cm of the cervix except under special circumstances The treatment in general begins with the application of radium It is repeated in three weeks and followed by rœntgen therapy to the parametrium from two back and two front portals

Complications Following Primary Therapy

The radium therapy was interrupted due to sepsis in five cases all of whom were dead within five years The intrauterine and intravaginal radium therapy was given at intervals in 12 cases in order to prevent undue trauma or sepsis during the implantation

Three patients developed slight bladder reactions and two slight rectal reactions

Remarks

Twenty-nine patients who failed to survive five years had clinical evidence of continued growth or recurrence during the six months following the beginning of therapy Eleven of these received additional therapy consisting of radiotherapy in six cases and electro-coagulation therapy in five cases Among the five year survivors three patients developed clinical evidence of recurrence or continued tumour growth during the six months following the beginning of therapy Two then received additional radiotherapy and the other received electro coagulation therapy

Twelve cases who failed to survive five-years developed recurrences between 6 months and 3 years after the beginning of therapy The recurrences were found on the pelvic wall or in the parametrium in 6, locally in one Both local and pelvic wall involvement was seen in 3 and distant metastases were present in 2 cases The patient with a local recurrence was treated by Wertheim hysterectomy Five patients received additional radiotherapy, two had colloidal gold injected into the parametrium and four received no additional therapy One of the five year survivals developed clinical evidence of local recurrence during the period between six months and three years following diagnosis and received electro-coagulation therapy

An additional case developed a local recurrence 9 years after the original therapy A modified Brunschwig operation was performed and she survived an additional five years before dying of cancer of the cervix

Results

Thirty-three of the 79 patients healed after primary therapy In 24 patients additional therapy was administered for recurrent or continued growth of the tumour Five of these 24 patients are five year survivors Thirty-six patients or 45 6 per cent of the 79 survived five or more years The survival rates according to stage were stage I 11 of 12 cases or 91 6 per cent, stage II 21 of 43 cases or 48 8 per cent, stage III 4 of 15 cases or 26 6 per cent and stage IV none of 9 cases or 0 per cent

Group 4 Carcinoma of the Cervix Diagnosed within 7 to 12 Months Following Pregnancy

This group of patients was not considered to be of particular significance in regard to the subject of carcinoma of the cervix associated with pregnancy, and is included only because it may be of some interest in relation to the total group of patients studied These cases are discussed very briefly

There were 78 cases diagnosed 7 to 12 months following pregnancy Six of these followed abortion and 72 were post partum They had an average duration of bleeding or of foul smelling discharge of 4 5 months These 78 cases were staged in accordance with the League of Nations classification as follows stage I 8, stage II 53, stage III 12 and stage IV 5 cases The configuration of the tumour lesions was that of a crater in 25, cauliflower in 24 and disc in 29 cases

The therapy administered to the patients in this group was in accordance with the Stockholm technique described in the dis cussion of Group 3 Thirty two cases or 41 0 per cent were five year survivors The survival rates according to stage were stage I 5 of 8 cases or 62 5 per cent, stage II 26 of 53 cases or 49 0 per cent, stage III one of 12 cases or 8 3 per cent and stage IV none of 5 cases or 0 per cent

Discussion

A study of 82 cases of invasive carcinoma of the cervix which occurred during pregnancy and 157 cases which occurred during the first 12 months following pregnancy It is based on material from the Radiumhemmet during the 24 year period 1932–56

The incidence of carcinoma of the cervix associated with pregnancy at the Radiumhemmet varies slightly from that noted at other institutions Reasons for slight variation in incidences have been mentioned

Twenty five of the 157 cases diagnosed during the post pregnancy period had the diagnosis made following an abortion Four of these 25 abortions were surgically induced one was a criminal abortion and one was an ectopic pregnancy The majority of the

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be influenced by the trimester of pregnancy, whether or not the patient has undergone labour and delivery, and the length of time after delivery when the carcinoma is diagnosed This accordingly necessitates an individual scheme of therapy for each case whilst keeping within a general plan of therapy for the different groups as presented in this study

The therapy used at the Radiumhemmet for cases of carcinoma of the cervix associated with pregnancy has changed over the years since 1914 During the first two decades a Wertheim hysterectomy was performed routinely in cases considered as oper able The results were unsatisfactory Subsequently Heyman introduced a combined therapy of surgery and irradiation This generally included a supracervical hysterectomy followed by intra cavitary radium therapy This combined method of therapy was tried in a small number of cases The results were unsatisfactory both with this combined method and with primary surgery As a sequel to the poor results obtained, a new technique of primary irradiation was introduced in 1932 The principle of this treatment has remained the same since that time Since this technique has been applied to a rather large series of cases of carcinoma of the cervix associated with pregnancy, it was felt worthwhile to report the Radiumhemmet s experience in these cases

There were 67 cases treated during the first two trimesters of pregnancy Treatment was begun with the intracervical and intra vaginal application of radium Cases received a high intensity of radiation which has always been included in the method of therapy at the Radiumhemmet The radium was left in place for about 25 hours in the average case Immediately after the radium was removed rœntgen therapy was begun through two to four an terior portals covering the pregnant uterus An attempt was made to avoid surgical interference with the pregnancy The majority of the patients underwent a complete and spontaneous abortion within an average of 29 days from the time of the beginning of therapy There were no cervical lacerations and no serious com plications associated with the abortion The patients received a second application of intra-cavitary radium about three weeks after the first application Approximately a week after the abortion additional rœntgen therapy was given toward the parametrium

other 19 cases are presumed to be spontaneous abortions The carcinoma was diagnosed within 6 months after abortion in 16 of these 19 cases and between 7 and 12 months following abortion in the other three cases The number of spontaneous abortions in this series is comparatively large There is no proof that the carcinoma was the causative agent in the abortion but this has been mentioned as a possibility previously by Danforth (1937), Prystowsky (1956) and Strauss (1940)

There is still disagreement among clinicians concerning the effect of pregnancy on the growth of the carcinoma of the cervix It is of interest that in this series the carcinoma diagnosed during the first two trimesters of pregnancy was generally at an earlier stage as compared with cases diagnosed in the period following pregnancy Thirty-nine of the 40 cases diagnosed during the first *trimester of pregnancy were in stage I or II Twenty-one* of the 27 cases diagnosed during the second trimester were in stage I or II The average duration of symptoms was 4 1 months in the first two trimesters and 4 4 months in the post pregnancy period The difference in regard to the duration of symptoms is therefore small The diagnosis of the carcinoma at a comparatively early stage during the first two trimesters may be due to routine examinations during pregnancy and also to the patients' increased alertness to symptoms During the last trimester of pregnancy the cases were diagnosed at a later stage Unfortunately this was partly dependent on an inadequate examination by the physician Three of the 15 cases diagnosed during the third trimester had been diagnosed and referred for therapy as placenta prævia Five other cases were diagnosed first during labour The longer period of symptoms in the post pregnancy groups was probably related to the interpretation of pathological discharge as being physiological The patients also had the calming psychological effect of a recent examination connected with the delivery and were less alert to signs of cancer

It was interesting to note that the configuration of the tumour lesions during pregnancy tended to be disc-shaped while in the post pregnancy period there was an increase in the cauliflower and crater type of lesions

The course of the disease of carcinoma of the cervix seems to

The five year survival rate for the total 239 patients treated was 46 9 per cent The five year survival rate for all cases of carcinoma of the cervix treated during this 24 year period was 45 5 per cent See Table II The five year survival rates for all cases according to stages were stage I 79 5 per cent stage II 52 2 per cent, stage III 26 8 per cent and stage IV 7 8 per cent

SUMMARY

A detailed survey is given of 82 cases of carcinoma of the cervix diagnosed during pregnancy and 157 cases diagnosed within 12 months after pregnancy All cases were treated during the 24 year period 1932–56 at the Radiumhemmet This period was selected because it supplies information regarding the five year survival rates of a group of patients treated by a standard method of therapy Prior to 1932 the cases of carcinoma of the cervix associated with pregnancy were treated by primary surgery or by primary surgery combined with irradiation therapy The results in those cases were very unsatisfactory There were 71 cases of carcinoma of the cervix diagnosed during pregnancy who received primary intra-cavitary radium therapy and external irradiation as the primary treatment of choice The five year survival rates of these 71 patients according to stages are stage I 74 3 per cent stage II 57 1 per cent stage III 25 per cent, and stage IV 0 per cent

The results were very poor in cases diagnosed during advanced pregnancy This series included only 12 such cases The primary therapy was radical surgery of Cæsarean section combined with irradiation therapy In two cases intravaginal radium therapy was given prior to the Cæsarean section but even in these two cases the results were unsatisfactory

The treatment for cases diagnosed during the first six months after pregnancy was irradiation The five year survival rates for the 79 patients in this group was 45 6 per cent The five year survival rates according to stages were stage I 91 6 per cent stage II 48 8 per cent stage III 26 6 per cent and stage IV 0 per cent

This was subject to slight variation depending on the clinical findings The five year survival rate for the 67 cases diagnosed during the first two trimesters was 59 7 per cent See Table I The five year survival rates for this group according to stages were Stage I 71 8 per cent, stage II 57 1 per cent, stage III 33 3 per cent and stage IV 0 per cent Since the number of cases is small, survival rates for the individual stages within each of the two trimesters are not given The five year survival rate for all cases diagnosed during the first trimester was 62 5 per cent and for those diagnosed during the second trimester, the survival rate was 48 1 per cent

The treatment for the 15 cases diagnosed during the third trimester of pregnancy varied throughout the years Therapy as detailed above was carried out in the three patients diagnosed during the early part of the third trimester All three of these patients are five year survivors Patients diagnosed during the last part of the third trimester could not be treated by this technique One case developed sepsis and died as a complication of the radium therapy This patient had a stage III carcinoma which was treated in the preantibiotic era Eleven cases were treated by different methods such as Cæsarean section followed by irradiation therapy and even by radical surgery combined with irradiation therapy Recently in two cases we have tried the application of intravaginal radium prior to Cæsarean section Unfortunately the results have been very poor and only one of these 11 cases has survived for five years

Patients diagnosed during the post pregnancy period received intra-cavitary radium and external irradiation therapy in accordance with the Stockholm technique Sepsis occurred during radium therapy in 13 of the 157 cases diagnosed during the 12 months following pregnancy There were 79 cases diagnosed during the 6 months following pregnancy and their five year survival rates according to stage were stage I 91 6 per cent, stage II 48 8 per cent, stage III 26 6 per cent and stage IV 0 per cent During the period 7 to 12 months following pregnancy there were 78 cases of carcinoma of the cervix diagnosed and their five year survival rates according to stage were stage I 62 5 per cent, stage II 49 0 per cent, stage III 8 3 per cent and stage IV 0 per cent

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Radiological Subcommission of the Committee on Hygiene of the League of Nations as expressed in its Annual Report (Case to be considered carcinoma of the vagina when the site of the growth is in the vagina, when the clinical examination shows the cervix is intact and when there are no grounds for supposing that the carcinoma is other than a primary growth in the vagina Cases in which the periphery of a more or less concentrically spreading vaginal mass encroaches upon the outside of the cervix *should also be classified as carcinoma of the vagina*) 145 cases were referred to the Radiumhemmet during this period Of this number 129 were examined and 12 of this group did not receive treatment An additional 16 cases were reported by letter but did not attend the clinic Treatment was carried out in 117 cases The status of the patients who were not treated is given in Table I Messelt (1952) reported that the incidence of carcinoma of the vagina among women over 25 years of age in Norway was 1 in 160,000 Because of the centralization at the Radiumhemmet of all cases occurring among almost 2/3 (actually 58 per cent) of the Swedish population, a similar analysis of the present material is permitted and thus reveals an incidence

Table I *Carcinoma of Vagina Cases not Treated*

Reason	Patients Examined at Radiumhemmet	Contact by Letter Only
Extensive cancer urinary or rectal fistula	3	5
Extensive cancer old age poor health	6	4
Extensive cancer plum sized inguinal node	1	2
Extensive cancer impending perforation	2	
Extensive cancer urinary retention		1
Referred to other clinic		2
Refused treatment	—	1
Dead before arrival	—	1

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From the Gynaecological Department Radiumhemmet, Stockholm, Sweden
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PRIMARY CARCINOMA OF THE VAGINA

A study of a Radiumhemmet Series of 145 Cases

BY

JAMES WHELTON* AND HANS LUDVIG KOTTMEIER

Introduction

The infrequency of carcinoma of the vagina and the concomitant paucity of cases treated at any one institution have long delayed an appreciation of the fundamental characteristics of this disease and hindered the development of an effective programme of management In the past decade publications based on relatively large number of cases have appeared from several clinics These have greatly augmented previous reports of this disorder However, the lack of a uniform clinical classification regarding the extent of the disease process before treatment has invalidated any attempt to compare the efficacy of methods of therapy employed at different clinics It is the purpose of this paper to suggest a clinical classification for carcinoma of the vagina and to evaluate the cases treated at the Radiumhemmet in accordance with this proposed staging

Material

The present study includes all patients referred to the Radiumhemmet between 1930–1955 with a diagnosis of carcinoma of the vagina These cases were in accord with the criteria of the

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nulliparous Palmer reported 28 4 per cent nulliparous patients in his series and Smith 30 4 per cent *In one case pregnancy* existed concomitant with a vaginal carcinoma

Symptoms

Eighty nine (76 per cent) of the patients had symptoms for 8 months or less, while only 3 were asymptomatic with the lesion discovered at routine examination The duration of symptoms is listed in Table III

Table III *Duration of Symptoms*

Time in Months	Patients
less than 2	29
3—5	34
6—8	23
9—11	6
12—14	12
15—23	5
24	4
unknown	1
asymptomatic	3
	117

Discharge and/or bleeding were the symptoms which prompted the patient to consult a physician in 97 (83 per cent) of the cases The majority of the cases with bleeding were post meno pausal Six instances of post-coital bleeding and 3 instances of intermenstrual bleeding occurred In 12 cases the presenting complaint was a "sore or lump" This occurred in the patients with prolapse or with lesions located in the lower 1/3 of the vagina Pelvic pain was the chief complaint noted in 5 cases

Nine cases (7 7 per cent) of vaginal carcinoma were associated with complete or 3rd degree prolapse The ages of these patients ranged from 50–80 years with an average of 68 years A pessary had been employed in 2 cases In both these cases the lesions were discovered at an early stage (maximum extent of growth 2 cm) before infiltration had taken place Both these growths

of 1 in 280,000 when the same criteria are used for calculation The average figure for females over 25 years of age in this region during the years studied was 1,575,000

During the same period (1930-1955) 7,601 cases of carcinoma of the cervix were treated, which gives a ratio of 65 1 with regard to treated vaginal carcinoma Smith (1955) reports a ratio of 34 1, Way (1948) 45 1, and Palmer (1954) 55 1 Primarily treated vulva carcinomas in this same period numbered 601 cases, giving a ratio of 5 2 1 Way reported 3 8 1 and Palmer 4 1

Age incidence

The age incidence among the treated patients is indicated in Table II The youngest patient was 24 years of age while the

Table II *Age Incidence*

Age	No of Patients	%
21 -30	4	3 4
31—40	15	12 8
41—50	21	18 0
51—60	26	22 2
61—70	30	25 6
71—80	18	15 4
81—90	3	2 6
	117	100

oldest was 82 The average age, 55 years, is in close agreement with other recent reports (Smith, Palmer, Messelt, Ries) One may conclude that carcinoma of the vagina reaches its highest incidence in the middle years of the sixth decade Sixty-six per cent of the patients in the present study were postmenopausal at the time the diagnosis of vaginal malignancy was made

Marital Status and Parity

Ninety four (80 per cent) of the patients had married and 25 per cent of this number were widowed Twenty two (19 per cent) had not married and in one case marital status was not known In the entire treated group 33 (28 3 per cent) were

and the patient was cured of her carcinoma (10 years without recurrence) This case is considered to be an example of *Zucker gusskrebs* (Schröder, 1959)

Reiffenstuhl (1957) has recently reviewed the work of previous authors and added observations from his own preparations on the lymphatic drainage of the female genitalia The lymph channels from the upper half of the vagina follow a pattern similar to that of the cervix as they course to the nodes on the pelvic wall The drainage from the lower half of the vagina likewise can follow this same route to the pelvic nodes or empty into the inguinal nodes through anastomoses formed by the lymph vessels of the vaginal mucosa cranial to the hymen and the lymph vessels of the vulvar region Direct anastomoses between lymph vessels in the vagina and the aortic lymph nodes are also described although these are not numerous Because of the thin wall and rich lymphatic drainage of the vagina Way (1948) believes that lymph node metastases occur early in the presence of malignancy and this explains the poor survival figures

Information as to the actual morbid anatomical changes associated with carcinoma of the vagina is regrettably limited In a detailed study of the pathological findings in eight surgical specimens Douglas (1954) found no evidence of lymph node involvement in 6 cases where lymph node dissection had been carried out Survival of the other two cases for more than 5 years was interpreted as evidence of only local disease (no radiation was given) Smith (1955) reports no nodal involvement in 17 patients who underwent radical surgery for carcinoma of the vagina at Memorial Hospital

In the present series of cases clinical examination under anæsthesia prior to treatment revealed the presence of a distinct mass on the pelvic wall in only two cases It cannot be concluded that lymph node metastases to the pelvic nodes occurred in only two cases but this finding is considered worthy of mention Palpation of the groins revealed clinically suspicious nodes in 8 cases The presence of metastases in the inguinal glands was confirmed by pathological examination in 4 cases Biopsy was not performed in the other 4 cases One patient in whom an inguinal gland was histologically positive had had a total hysterectomy 15 years

were papillary in character though a small central ulceration was present in one case There was no definite correlation with the use of a pessary Six of the cases with prolapse revealed large (average size 7×4 cm) superficially infected ulcerations with firm, slightly elevated edges In the final patient with prolapse the tumour measured 4×4 cm and showed minimal ulceration

Institution or proper therapy by the attending physician was delayed in 6 cases (5 1 per cent) One of these cases was the patient who was pregnant This patient was admitted on two occasions during the sixth and seventh months of gestation because of bleeding Pain in the right buttock was also present Caesarean section was subsequently carried out for presumed placenta praevia In the immediate postpartum period before discharge from the hospital a large vaginal carcinoma fixed to the right pelvic wall was discovered

Pathology

Over one half of the cases presented a significant ulceration in the vaginal wall The majority of these were penetrating with raised firm borders and at times associated nodularity The ulceration in a few instances was confined to the vaginal wall and little reaction in the surrounding tissue was observed

Papillary growth was the chief feature in 30 per cent of the carcinomas These lesions may be well defined on a broad based stalk or less frequently involve the vaginal wall without significant demarcation In general they have a soft consistency and small lesions may be missed on palpation Routine visual inspection of all the walls of the vagina with the aid of a speculum insures prompt discovery In 15 cases the tumour presented as an elevated plaque, well demarcated without ulceration and of firm consistency Eight carcinomas extended in diffuse fashion subepithelially with little or no ulceration of the vaginal mucosa Because of their firm consistency they can readily be detected by recto-vaginal examination when they are located in the recto vaginal septum In one case the entire vaginal mucosa was involved by a tumour described grossly as having a cobble stone appearance No infiltration was noted beyond the vaginal wall

It is seen that 53 (45 per cent) growths occupied a posterior or postero lateral position In the lower third of the vagina the lateral position, 9/20 (45 per cent) was more frequently the site of origin

Smith (1955) has suggested that lesions above the lower 1/3 of the vagina have a better prognosis In the present series 9 of 20 cases (45 per cent) in the upper 1/3 survived 5 years There were 5 out of 12 five year survivors (42 per cent) with lesions restricted to the middle third Of the 20 cases occurring in the lower 1/3 of the vagina 5 involved the labia minora or the clitoris If these cases are excluded (all died of disease) the five year survival among cases in the lower 1/3 is 4 out of 15 (27 per cent) However if the growths involving the upper 2/3 of the vagina are reviewed these show a survival figure of 5 out 23 (21 5 per cent) whereas the growths occupying the lower 2/3 of the vagina have 5 out of 17 (29 5 per cent) No certain conclusions can be drawn because of the small numbers in each group but location does not appear to offer a reliable index for prognosis

Classification

A critical approach to the management of malignant disease requires the use of some uniform system of classification of the clinical extent the disease in every institution which undertakes the therapy of cancer cases A review of publications dealing with carcinoma of the vagina confirms the efforts of investigators to achieve this aim Several authors have employed a division into two groups with the designations restricted and extensive or localized and advanced" (Smith Ries, Palmer, Messelt) Courtail utilized a classification with 3 stages and Kahanpää evaluated his cases in 4 stages Each author carried out his analysis according to the details given in the individual publication but the lack of uniformity among these criteria does not permit a comparison between the case material and hence the therapeutic results obtained at the different institutions are not comparable

The success and acceptance achieved by the international classification for cervical carcinoma suggests that these concepts could

previously The cancer of the vagina was located in the upper 1/3 and it is possible that the metastases occurred via the lymphatics of the round ligament

Microscopic Pathology

Biopsies of the vaginal tumour were made in each case, 112 were stratified squamous carcinoma, 3 were adenocarcinoma and 2 were poorly differentiated solid carcinoma One of the latter was probably stratified squamous but the section was too small to determine this The other poorly differentiated lesion had the appearance of a transitional cell carcinoma' and was remarkable for the enormous number of eosinophils which infiltrated the stroma about the carcinomatous growth In the 3 cases which revealed an adenocarcinoma the scrapings from the uterine fundus were negative No adnexal masses could be palpated to suggest an ovarian primary in these cases Not included in this series is a most unusual basalioma which will be published in a separate report

Location of Growth

Locations of the lesions are presented in Table IV

Table IV *Location of Growth*

	Upper 1/3	Middle	Lower	Upper 1/2	Lower	Entire	Total
Po terior	7	4	2	7	4	2	26
Anterior	2	4	2	2	1	2	13
Lateral	3	—	9	1	3	—	16
Antero-lat	1		3	1	1	4	10
Postero-lat	4	4	1	7	6	5	27
3/4 circumfer	2	1		5	2	9	20
Entire	1	—	1	—	—	3	5
	20	13	19	23	17	25	117

the patient Ledermann (1942) has stated that any method of local radium application for carcinoma of the vagina must take into account the precise site of origin of the lesion, its possible maximal vaginal extent and the presence or absence of involvement of adjacent structures such as the cervix, rectum, vulva, urethra, bladder or rectum He recommends the construction of an applicator based on an impression of the vaginal growth itself in the specific case At the Radiumhemmet this individual approach is achieved by a wide variety of applicators Flat and curved boxes as well as cylindrical devices are available For each of these types various sizes exist and are so constructed as to permit variation in the geometrical arrangement of the radium sources An effort is made to cover the entire surface of the tumour, with the radium sources spread out as much as possible to avoid overdosage to any one point If a large exophytic lesion is present external therapy may be employed first to shrink the growth and ensure a better application of the radium Careful gauze packing is essential to maintain the applicator in position against the tumour and to prevent displacement which could produce injury to neighbouring structures

The evolution of radium therapy developed empirically High concentrations of radium sources (60–100 mg) were employed for relatively short exposure periods (18–22 hours) The filtration was equivalent to 3 mm of lead Both intravaginal and intra uterine radium were employed in 79 per cent (92/117) of the cases In 18 per cent (22/117) intravaginal radium only was applied the intravaginal dose averaged 3400 mg hr with the intrauterine "dose varying from 1,250–2 800 mg hr Clinical circumstances such as poor general condition, impending perforation sepsis pronounced reaction to first radium treatment, persistence of disease etc modified the treatment in the individual case In July 1953 routine measurements were commenced with a dosimeter that could be placed in the bladder and rectum This permitted a more objective appraisal of dosage given in the individual case but in this study the number of cases in which figures were available is too small to permit any conclusions to be drawn

Supplementary external radiation was employed in 89 0 per

be modified to furnish a practical standard for the evaluation of the clinical extent of vaginal carcinoma Through the medium of "*The Annual Report on the Results of Treatment in Carcinoma of the Uterus*" the collected experiences of 78 institutions from various sectors of the world furnish information on almost 100,000 treated cases of carcinoma of the cervix The significance and value of this data is obvious

The following classification is presented with the hope of stimulating discussion which may ultimately achieve a parallel success for carcinoma of the vagina An objection may be proposed that the infrequent occurrence of vaginal malignancies does not merit so detailed a staging In fact, the paucity of cases at any one clinic underlines the necessity for close cooperation to promote the advance of knowledge in this area

Clinical Classification of Carcinoma of the Vagina

Stage I		The carcinoma involves 2 cm or less of the vaginal mucosa
Stage II	A	The carcinoma involves more than 2 cm but less than the entire vaginal mucosa in the longitudinal axis
	B	The carcinoma infiltrates the paracolpos but does not reach the pelvic wall
Stage III	A	The carcinoma involves the entire vaginal mucosa in the longitudinal axis
	B	The carcinomatous infiltration extends to the pelvic wall and is fixed there
Stage IV	A	The carcinoma involves the bladder, urethra, rectum or vulva
	B	The carcinoma extends outside the true pelvis, *i e* metastases to the inguinal lymph nodes, to nodes above the pelvic brim or distant metastases

Therapy

The scheme of treatment in each case was individualized according to the extent of the disease and the general condition of

Results

The survival period for the treated cases is presented in Table VI Seventy-seven patients (65 8 per cent) died within 3 years

Table VI *Survival Period for Treated Cases*

Time from Treatment	Dead	Survivors	Survivors
less than 1 year	40	77	65 8
over 1 year — less than 2 years	24	53	45 3
over 2 years — less than 3 years	14	39	33 4
over 3 years — less than 4 years	4	35	29 9
over 4 years — less than 5 years	4	31	26 5

from the time of treatment Six patients of this group died from intercurrent disease Among the 31 patients who had survived for five years 8 subsequently died from vaginal carcinoma (2 patients between 5-6 years, 3 patients between 8-9 years, 2 patients between 9-10 years and 1 patients at 14 years) A total of 88 patients (75 2 per cent) died from the vaginal carcinoma the longest interval between treatment and death being 14 years

Table VII presents the results obtained when the cases are staged in accordance with the recommendations given above

Table VII *Correlation of 5 Year Survival with Clinical Staging*

Stage	Number of Cases	Dead of Cancer	Inter-current Death	5 Year Survivors	5 Year Survivors
I	10	3	2	5	50 0
II A	31	17	2	12	38 7
II B	15	10	2	3	20 0
III A	2	1		1	50 0
III B	45	36	—	9	20 0
IV A	10	9		1	10 0
IV B	4	4	—		0 0
	117	80	6	31	26 5

cent (104/117 cases) Both high energy beams and conventional roentgen rays were used With the teleradium unit 3,000–4,000 r were directed towards the vulva particularly in those cases where the lesion was in the lower part of the vagina Similar dosages were given to the groins Since 1951 a cobalt unit replaced the teleradium-apparatus Conventional therapy with a 170 KV machine was employed for treatment of the paracolpos and lateral pelvic walls (additional factors Thoraeus filter or 0 5 mm copper, 15 mA, focus skin distance 50–70 cm, half value layer of the radiation 0 8 mm of copper) The radiation was given through two anterior and two posterior fields with 400 r delivered 4–6 times through each of the four portals In a few instances the external radiation consisted of 400 r delivered 5 times to large opposing anterior-posterior fields in the pelvis

Primary healing of the carcinoma was achieved in 60 patients (51 2 per cent) with the disease uncontrolled after treatment in 57 In the cases which exhibited clinical healing 52 of the 60 patients (86 5 per cent) demonstrated no clinical evidence of disease within 4 months from the onset of therapy Table V shows the relationship between the modalities of treatment and response of the disease

Table V *Mode of Therapy and Clinical Result*

Mode of Therapy	Primary Healing	Primary Healing with Recurrence	No Healing
Radium (vaginal alone or with intrauterine) No external radiation	4	5	3
Vaginal radium + external radiation	5	5	-
Vaginal and intrauterine radium + external radiation	16	22	44

(These cases total 111 In 2 of the other 6 cases no radium was used — only external radiation in one case of prolapse intrauterine radium was used with external therapy The remaining 3 cases had electro-coagulation in addition to one of the listed modes of therapy)

vals commencing with the fifth year Exceptions to this general programme occur at times because of long distances (over 600 miles to distant points in northern Sweden) and old age with disability (arthritis, heart disease etc)

A recurrence was defined as the presence of carcinoma after a minimum of two follow up examinations had shown no evidence of disease Severe pain in the hip or thigh considered as recurrent disease even if palpable evidence of disease was not present (2 cases) Thirty three of the 60 patients (55 per cent) who had primary healing of the carcinoma developed a recurrence Observations with regard to the time, symptoms and location of the recurrences are summarized in Table IX

Table IX. *Observations with Regard to Time Symptoms and Location of Recurrence*

Time in Months from Start of Treatment	No of Patients	Symptoms	No of Patients	Location	No of Patients
3—6	7	Bleeding and/or discharge	13	Vagina Local	11
7—9	4	Hip or leg pain	4	Extensive	6
10—15	4	Enlarged inguinal node	2	Pelvic wall Inter iliac	3
16—25	4	Cystitis	1	Superior glutei	1
26—35	3	Labial swelling	1	Common iliac	1
35—45	3	Large liver	1	Inguinal	2
Over 46	3	Weight loss fatigue	1	Pelvic tumour + ascites	1
Unknown	5	Leg swelling	1	Metastatic to liver	1
		No symptoms	4	Unknown	7
		Unknown	5		
	33		33		33

Fifty-eight per cent (19/33) developed the recurrence within 2 years In 3 patients the recurrence first appeared after 5 years, in one of these after almost 14 years Bleeding and/or discharge occurred as the primary symptom in over 1/3 of the cases Hip or leg pain as the initial symptom was present in 4 cases with an additional patient showing leg swelling 4 cases of recurrence

It can be seen that the occurrence of a few intercurrent deaths is sufficient to alter significantly the percentage of survivors when the total numbers of cases in a stage is small Cure of the carcinoma, *where infiltration had not taken place*, (stage I, II A, III A), was achieved in 41 6 per cent (18 out of 43 cases) If infiltration had occurred (II B, III B, IV A and B) cure was obtained in only 17 6 per cent (13 out of 74 cases) Only 2 of 25 cases where the entire mucosa in the longitudinal axis of the vagina was involved did not have infiltration

The relative five-year survival was 26 5 per cent If the 12 patients, who were examined at the hospital but did not receive treatment are added, an absolute five-year survival of 24 1 per cent was obtained

The relative survival for patients followed up for 10 years or longer was 16 9 per cent The absolute survival for ten years was 15 3 per cent.

A comparison with results at other clinics is given in Table VIII

Recurrences

The follow-up policy at the Radiumhemmet permits observations to be made with regard to recurrences In the first year following treatment patients are examined each month, in the second year every other month, in the third year every third month, each fourth month during the fourth year and at 6–12 month inter-

Table VIII *Comparison of End Results at Different Clinics*

Author	Years Study	Total Cases Exam	Treated Cases	Treated >5 Yrs	Relative 5 Yrs Survival	% 5 Yrs Relative Survival	% 5 Y Absol. Surv
Huber (1950)	1922—1949	152	134	104	18	16 4	16 4
Messelt (1952)	1932—1945	78	78	78	17	22 7	22 7
Ries (1953)	1933—1943	130	129	129	30	23.4	23 1
Palmer (1954)	1919—1952	112	112	75	24	32 0	32 0
Smith (1955)	1927—1946	109	109	109	34	31 1	31 1
Radiumhemmet (1960)	1930—1955	129	117	117	31	26 5	24.1

vals commencing with the fifth year Exceptions to this general programme occur at times because of long distances (over 600 miles to distant points in northern Sweden) and old age with disability (arthritis, heart disease etc)

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Over 46	3	Weight loss fatigue	1	Pelvic tumour + ascites		1
Unknown	5	Leg swelling	1	Metastatic to liver		1
		No symptoms	4	Unknown		7
		Unknown	5			
	33		33			33

Fifty-eight per cent (19/33) developed the recurrence within 2 years In 3 patients the recurrence first appeared after 5 years, in one of these after almost 14 years Bleeding and/or discharge occurred as the primary symptom in over 1/3 of the cases Hip or leg pain as the initial symptom was present in 4 cases with an additional patient showing leg swelling 4 cases of recurrence

It can be seen that the occurrence of a few intercurrent deaths is sufficient to alter significantly the percentage of survivors when the total numbers of cases in a stage is small Cure of the carcinoma, where infiltration had not taken place, (stage I, II A, III A), was achieved in 41 6 per cent (18 out of 43 cases) If infiltration had occurred (II B, III B, IV A and B) cure was obtained in only 17 6 per cent (13 out of 74 cases) Only 2 of 25 cases where the entire mucosa in the longitudinal axis of the vagina was involved did not have infiltration

The relative five-year survival was 26 5 per cent If the 12 patients, who were examined at the hospital but did not receive treatment are added, an absolute five-year survival of 24 1 per cent was obtained

The relative survival for patients followed up for 10 years or longer was 16 9 per cent The absolute survival for ten years was 15 3 per cent

A comparison with results at other clinics is given in Table VIII

Recurrences

The follow-up policy at the Radiumhemmet permits observations to be made with regard to recurrences In the first year following treatment patients are examined each month, in the second year every other month, in the third year every third month, each fourth month during the fourth year and at 6–12 month inter-

Table VIII *Comparison of End Results at Different Clinics*

Author	Years Study	Total Cases Exam	Treated Cases	Treated >5 Yrs	Relative 5 Yrs Survival	% 5 Yrs Relative Survival	% 5 Yrs Absolute Survival
Huber (1950)	1922—1949	152	134	104	18	16 4	16 4
Messelt (1952)	1932—1945	78	78	78	17	22 7	22 7
Ries (1953)	1933—1943	130	129	129	30	23 4	23 1
Palmer (1954)	1919—1952	112	112	75	24	32 0	32 0
Smith (1955)	1927—1946	109	109	109	34	31 1	31 1
Radiumhemmet (1960)	1930—1955	129	117	117	31	26 5	24 1

was responsible for 10 of the fistulae, radiation therapy for two and in one case the cause could not be determined

Twelve radiation reactions occurred in the patients Eight of these were located in the rectum (3 mild, 2 moderate, 3 severe) Two of the patients who sustained severe reactions had pre viously been diagnosed as suffering from pernicious anæmia In one instance the reaction process was very diffuse with pronounced symptoms and in the other patient the reaction was complicated by erysipelas pelvic infection and recto vaginal fistula

In 4 cases diffuse pelvic infections followed application of the radium These patients survived for an average of 7 months whereas the patients in whom the disease was not controlled but who did not exhibit signs of pelvic infection survived for an average of 13 months

Two instances of trauma occurred In one case a rupture of the posterior vaginal wall occurred and in the other a perfora tion of the uterus was made during curettage

Conclusions

Between the years 1930–1955 145 patients with a diagnosis of carcinoma of the vagina were referred to the Radiumhemmet Of this number 129 patients were examined and 12 patients were not treated An additional 16 cases were reported by letter but did not attend the hospi al The data in the present study is based on the charts of the 117 treated cases

The study confirms that careful investigation of the vagina is an essential part of every pelvic examination This requires the use of a speculum to inspect the vaginal walls as well as vaginal and recto vaginal palpation In the gravid patient with bleeding vaginal examination must be performed to rule out pathological conditions unrelated to pregnancy

The present state of knowledge concerning the morbid changes associated with carcinoma of the vagina is limited The vagina has an extensive network of lymphatics but no statement can be made at present as to the frequency of lymph node metastases From clinical obeservation it would appear that the cause of

were noted at the time of follow-up examination in patients who did not have any symptoms

The distribution of recurrences indicated a tendency for the disease to recur locally, either within the limits of the vagina or as a large tumour extending from the vagina to one or both of the pelvic walls (17 of 33 cases – 51 1 per cent) In 5 cases recurrence was noted as an enlargement of the pelvic wall lymph nodes In 2 instances the inguinal nodes were the first observed site for recurrence In 7 cases initial area of involvement could not be determined

Table X lists the therapy employed for these recurrences

Table X. Treatment of Recurrences

Mode of Treatment	Number of Patients
None	13
Electro-fulguration	8
X ray	5
Local radium	4
Teleradium	3
Total	33

One case with a local vaginal recurrence re-treated by local radium lived 18 years free of disease In another case a local recurrence after 4 years was treated by electro fulguration, and this patient has gone 14 months without evidence of recurrence In two additional cases control of recurrent disease in the vagina was achieved by electro-fulguration (plus radium in one case) for 6 years before the patients succumbed to the disease Thus 1 patient was cured and another patient was free from carcinoma over one year after treatment for recurrence Thirty-one of the 33 cases with recurrent disease died from the carcinoma

Complications

Complications appeared in 25 per cent of the cases There were 13 *fistulae* which developed after therapy, one was vesico vaginal and 12 were recto vaginal Progression of the carcinoma

was responsible for 10 of the fistulae, radiation therapy for two and in one case the cause could not be determined

Twelve radiation reactions occurred in the patients Eight of these were located in the rectum (3 mild, 2 moderate, 3 severe) Two of the patients who sustained severe reactions had previously been diagnosed as suffering from pernicious anæmia In one instance the reaction process was very diffuse with pronounced symptoms and in the other patient the reaction was complicated by erysipelas, pelvic infection and recto vaginal fistula

In 4 cases diffuse pelvic infections followed application of the radium These patients survived for an average of 7 months whereas the patients in whom the disease was not controlled but who did not exhibit signs of pelvic infection survived for an average of 13 months

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Conclusions

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The present state of knowledge concerning the morbid changes associated with carcinoma of the vagina is limited The vagina has an extensive network of lymphatics but no statement can be made at present as to the frequency of lymph node metastases From clinical obcservation it would appear that the cause of

death in the majority of cases can be attributed to local spread of the disease with secondary complications such as hemorrhage, anæmia, infection, pain etc rather than a generalized spread of the carcinoma

A classification for carcinoma of the vagina analogous to the international staging for carcinoma of the cervix is presented The employment of such clinical evaluation would permit a satisfactory comparison between case material and results ob tained at different clinics which is not possible at present

Treatment in the present series was with radiation In 2 cases local excision was carried out before radiation was given In the majority of cases both brachyradium and external therapy was employed In 79 per cent of the cases, the radium was applied both in the vagina and uterus

Primary healing of the disease was achieved in 60 patients (51 2 per cent) This occurred within 4 months from the onset of therapy in 52 cases (86 5 per cent) Disease persisted after treatment in 57 case (48 8 per cent) The average length of life for these patients was 13 months

Recurrences occurred in 33 of the 60 patients (55 per cent) who had shown primary healing The recurrence appeared within 2 years from the time of treatment in 19 cases (58 per cent) In 3 cases the carcinoma recurred after 5 years, the longest interval being 14 years after therapy The vagina was the site of the recurrence, either local or diffuse, in over one half of the cases Only one case with recurrent disease was cured In 2 cases the recurrences were controlled for 6 years before the patients died from cancer One other case is at present free from disease 14 months after treatment for a recurrence Extensive electro ful- guration appeared to offer the most effective management for recurrence in the vagina

Fistula was the most frequent complication after treatment but in most instances it could be attributed to progression of the disease (10 of 13 cases) Radiation reactions were noted in 12 cases 2 patients with previously diagnosed pernicious anæmia had severe rectal reactions Diffuse pelvic infection appeared to have a deleterious effect on survival time in 4 patients

The relative five-year survival rate was 26 5 per cent and the

absolute five year survival 24 1 per cent For patients followed up for 10 years the relative survival was 16 9 per cent The corresponding absolute figure was 15 3 per cent

SUMMARY

The paper considers 145 cases of carcinoma of the vagina referred to the Radiumhemmet between the years 1930–1955 One hundred and twenty nine cases were examined at the hospital and 12 of these cases did not receive treatment Sixteen cases were reported by letter but did not attend the hospital The clinical extent of the disease prior to treatment in 117 cases was evaluated by grouping these cases into four stages analogous to the International Classification for carcinoma of the cervix Treatment was by radiation, usually with a combination of brachyradium (often both in the vagina and uterus) and external therapy Primary healing occurred in 60 patients but of this number 33 developed recurrence Thirty-one of these cases died from the recurrent disease The relative five year survival rate was 26 5 per cent, the absolute was 24 1 per cent. The corresponding figures for patients followed up for ten years was relative 16 9 per cent, absolute 15 3 per cent Complications occurred in 25 per cent of the treated cases and included fistulae (mostly due to progression of disease), radiation reactions, pelvic infection and trauma

Acknowledgement

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SERUM COPPER DETERMINATIONS IN NORMAL PREGNANCY AND ABORTION

BY

F HEIJKENSKJÖLD AND S HEDENSTEDT

The causes underlying the failure of a pregnancy and subsequent abortion were previously obscure Lately, mechanical factors and disturbances in endocrine balance during pregnancy have been identified as contributory causes of abortion The endocrine regulation of pregnancy has been closely investigated by a number of authors during later years It has been found that the placenta produces gonadotrophin, progesterone, and œstrogens, all of which are necessary to normal pregnancy The placenta also produces the enzyme histaminase (Ahlmark 1944 Kapeller Adler 1950) which breaks down histamine Detailed studies by Ahlmark (1944) Svanberg (1948) and Genell (1950) have shown that histaminase analyses provide the most sensitive indicator of the normal course of pregnancy and that histaminase determinations give the best guide to prognosis in cases of threatened abortion

Holmberg and Laurell (1950 and 1951) identified an enzyme in the serum so-called cæruloplasmin an alpha globulin with a molecular weight of 151 000 isolectric at a pH of 4 4 and with a copper content of 0 34 per cent Ninety six per cent of the total copper content of the serum is bound to cæruloplasmin This enzyme has a strong oxidizing effect upon para phenylendiamine para aminobenzoic acid histamine, and epinephrine These authors also investigated the copper content of the serum and

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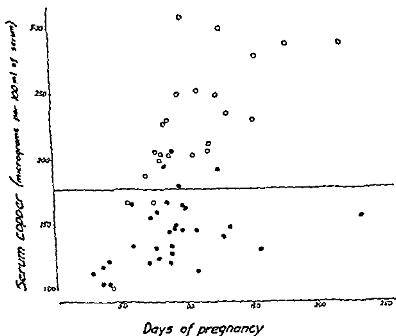


Fig 1 Serum copper values in normal pregnancies and threatened abortions of favourable prognosis are indicated with circles (○) Serum copper values in spontaneous abortions and threatened abortions with negative results are indicated with filled circles (●) The horisontal line represents the mean value for all analyses (177 microgram Cu/100 ml serum)

value was 225 micrograms of copper per 100 ml of serum (n = 23)

Discussion

Analyses of histaminase, progesterone, and gonadotrophin have been used as aids in evaluating the prognosis in threatened abortion Gonadotrophin analyses can be made with the aid of various experimental animals (for further details see Diczfalusy 1953) A disadvantage of these tests, however is that they are fairly expensive and demand a constant supply *of experimental animals* Progesterone analyses are usually carried out on the urine, the excretion of pregnanediol being determined As this test requires a

pointed out that a direct relation is demonstrable between t
oxidizing ability of the serum and its copper content, and th
both increase during pregnancy

The connection between the serum copper level and aborti
has not previously been investigated, as far as we can discov
in the literature The aim of the present study was to try
ascertain whether determination of the serum copper level cou
afford a simple guide to prognosis in cases of threatened abortio

Material and Methods

Blood samples were taken with a platinum needle in the mor
ing while the patient was fasting (Munch-Petersen 1950
After centrifuging – without metal contamination – the seru
was separated into specially prepared tubes and sent to the Ce
tral Chemical Laboratory of Allmanna Sjukhuset in Malmo f
analysis of serum copper Samples of blood from patients in who
abortion threatened or was inevitable, patients with normal pre
nancies admitted to hospital for legal abortion, and one patie
suffering from hydatidiform mole were examined

Results

It will be seen in Fig 1 that the serum copper values in therater
ed abortion of poor prognosis were appreciably lower than thos
in normal pregnancy and in threatened abortion of favourabl
prognosis The values in spontaneous abortions ranged from 10
to 205 micrograms of copper per 100 ml of serum, the corre
sponding durations of pregnancy were 75 to 235 days In threat
ened abortion with a positive biological pregnancy test and sub
sequent completed pregnancy, and in normal pregnancy, th
values ranged from 101 to 307 micrograms of copper per 100 m
of serum The duration of pregnancy varied from 71 to 156 days
The mean value for the whole series was 177 micrograms o
copper per 100 ml of serum (n = 55), while in spontaneous an
threatened abortion with negative results the mean value wa
142 micrograms per 100 ml of serum (n = 32) In normal preg
nancy and threatened abortion of favourable prognosis the mean

A 27 year-old woman with characteristic symptoms of pregnancy had a hæmorrhage 95 days after her last menstruation She was admitted to hospital with a diagnosis of threatened abortion and given the usual prophylaxis A serum copper test showed an abnormally high value, 295 micrograms per 100 ml of serum The bleeding stopped and she was sent home She was readmitted with a fresh hæmorrhage 112 days after the last menstruation The cervix was found to be patent and the uterine cavity was evacuated a hydatidiform mole was present, but no fœtus The serum copper level had risen further to 433 micrograms per 100 ml of serum The usual hormone titration of chorionic gonadotrophin in the urine showed a high value 1,400 international units HCG A repeated serum copper determination 160 days after the last menstruation showed a value of 161 micrograms per 100 ml of serum Concurrent hormone titration gave a considerably lower value 400 international units HCG

This case prompts the conclusion that a hydatidiform mole, by its effect on copper metabolism, gave rise to an abnormally high copper value which returned to normal after removal of the mole It would seem that the increase in the production of chorionic gonadotrophin and œstrogens frequently associated with hydatidiform mole may have led to the rise in the serum copper level

In another patient a 31 year old woman uterine hæmorrhage occurred 90 days after the last menstruation and prophylactic treatment for threatened abortion was given The serum copper value was 229 micrograms per 100 ml of serum The patient s bleeding was continuous but very slight Determination 97 days after the last menstruation showed a copper value normal for pregnancy 249 micrograms per 100 ml of serum and after 112 days 251 micrograms per 100 ml of serum Repeated pregnancy reactions were positive From this it may be concluded that the threatened abortion was of favourable prognosis as demonstrated by the positive pregnancy tests and the serum copper content which was within normal limits for pregnancy

An increased copper content in the serum during pregnancy has previously been demonstrated by Nielsen (1944) de Vries (1953) and others Methodical examinations by Gisinger (1955) have shown an increase in the serum copper level not

24 hour volume of urine and the chemical analysis is complex, it *is impossible to expect a quick answer when evaluating the prob* able outcome of a threatened abortion Histaminase analyses are rather complicated and require the resources of a large laboratory However, it is generally considered that they afford the most reliable basis for a prognostic assessment Analyses of histaminase and progesterone (pregnanediol in the urine) have been used by Borglin and Willert (1957 and 1960), among others, these methods enabled them to forecast 98 per cent unfavourable out comes in women with threatened abortion

Huggett and Pritchard (1945), Cassmer (1959), and others have shown that when the communication between the *fœtus and the placenta is interrupted, the production of œstro*gens by the placenta quickly decreases while that of progesterone and gonadotrophin is not affected This may be taken to imply that the production of the hormones used in evaluating the prognosis of abortion is continued as long as the communication be tween the placenta and the fœtus is not interrupted In the cases labelled spontaneous abortion in Fig 1, the patients had undergone operative evacuation of the uterine cavity and no hormone analyses were made One patient had a spontaneous abortion after 115 days of pregnancy and expelled a fœtus, but no placenta was discharged As there was no very pronounced vaginal bleeding it was decided to postpone the evacuation of the uterine cavity Three days later the patient had a slight hæmorrhage, the uterine cavity was then evacuated and the placenta removed The serum copper level was determined on expulsion of the fœtus and was high, 279 micrograms per 100 ml of serum Earlier in her preg nancy, however, an isthmic insufficiency had been detected with dilatation of the whole cervical region sufficient to allow the pas sage of a finger The serum copper value lay within the limits for a normal *pregnancy, but mechanical factors were responsible for* the abortion in this instance The endocrine production of the placenta was in all probability intact This permits the conclusion that the elevation of the serum copper level in pregnancy is attributable to the normal blood supply of the *placenta via the* uterus The influence of the placenta upon copper metabolism during pregnancy is best illustrated by the following case

elevated in normal pregnancy and threatened abortion of favourable prognosis In one case of hydatidiform mole the copper value was extremely high as long as the mole tissue remained in the uterus However, the small size of the series permits no definite conclusions as to the value of serum copper determination in threatened abortion

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only in pregnancy but also in infections, malignant tumours, Hodgkin's disease, acute myeloma, lymphatic leukaemias, obstructive jaundice, and cholangitis The same author found low values in hypoproteinaemia, schizophrenia, and familial hæmolytic jaundice as well as in cirrhosis of the liver and hæmochromatosis Parallel investigations of serum iron had not revealed any relation between the copper and iron contents of the serum

Russ and Raymunt (1956) and Humoller *et al* (1960) have shown that the administration of œstrogens to healthy persons and to patients suffering from carcinoma of the prostate leads to an increase in cœruloplasmin and in the serum copper content, respectively Their experiments would appear to suggest that the increased production of œstrogens during pregnancy leads to a rise in the serum copper level, but no experimental studies are available at present concerning the effect of other pregnancy hormones on the metabolism of copper

The results reported above suggest that the serum copper content is low in abortion, and that the placenta is essential to the increase in serum copper found in normal pregnancy Tests carried out in a case of hydatidiform mole suggest that the serum copper content is influenced by the production of chorionic gonadotrophin or of œstrogens The histaminase value associated with hydatidiform mole is within normal limits for pregnancy (Willert 1953)

The oxidative activity of blood serum thus increases during pregnancy due to an increase of histaminase and cæruloplasmin Whether these enzymes have some factor in common is not known but it is striking that both seem to diminish in cases of endocrine abortion

The present series is small Further studies in a larger number of cases are necessary before appraising the reliability of serum copper determinations as a tool in the prognosis of threatened abortion

SUMMARY

The serum copper level was determined in cases of abortion, normal pregnancy, and in one of hydatidiform mole A fairly low copper value was found in spontaneous abortion, while it was

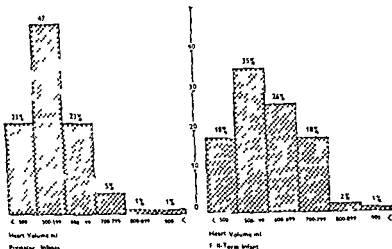


Fig 1 Percentage Distribution of Maternal Heart Volume after Parturition

Material and Methods

The material consisted of 80 mothers of premature infants and 80 mothers of full term infants All children weighing 2500 g or less were classified as premature The mothers of the full term infants were randomly selected Only normal pregnancies were included in the series Multiple pregnancies were not included The women examined represent a uniform cross-section of all classes of society of Gothenburg

The heart volume of the mothers was determined roentgenologically with the Liljestrand-Lysholm-Nylin-Zachrisson-method, modified by Jonsell (1939) *i e* the same method as used at the Women s Clinic in Helsingfors The weight of the mother and the duration of pregnancy were also noted.

Results

The percentage distribution of the maternal heart volumes is shown in Fig 1

In comparison with a similar figure in a publication of Unnérus (1959) our series shows the same distribution between

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MATERNAL HEART VOLUME AND PREMATURITY

BY

E HEDBERG AND C RÅDBERG

Modern obstetric statistics show that prematurity is one of the principal causes of neonatal mortality About 50 per cent of still born infants are premature The reduction of perinatal mortality due to prematurity primarily involves the obstetrician In general, the longer the fœtus can remain in the uterus, the better are its chances for extrauterine survival, as the mortality rate of premature infants is inversely related to their birth-weights The ætiology of prematurity is, however, still obscure Obstetric inquiry over the last decade has shown that about 50 per cent of all premature births are caused by multiple pregnancy, ante partum hæmorrhage and pregnancy toxæmia For the remaining 50 per cent no known cause for the premature labour could be ascribed, though it is probable that economic and social factors play a significant part

During recent years some interesting results concerning the ætiology of prematurity have been published from the Women's Clinic in Helsingfors According to these papers there seems to be a relationship between the heart volume of the mother and the birth weight of the infant (Raiha *et al*, 1956, Unnerus, 1959)

As the problem is of current interest we decided to start a similar investigation at the Women's Clinic I in Gothenburg The first part of this investigation was a study concerning the relationship between the maternal heart volume two days after parturition and the birth-weight of the child

d the duration of pregnancy is recorded for different groups of aternal heart volumes

ble III *Maternal Heart Volume in Relation to Weight of Infant Weight of Mother and Duration of Pregnancy Mean Values*

Maternal Heart Volume ml	<500	500–599	600–699	700–799
Weight of Infant g	2573	2716	2868	3370
Weight of Mother, kg	55	59	66	71
Duration of Pregnancy days	262	265	267	269

From the table it is evident that the duration of pregnancy is about the same for the different groups but that there seems to be some relation between the three factors – maternal heart volume, maternal weight and birth weight of the child

In Table IV the case material is grouped according to maternal weight

Table IV *Weight of Mother in Relation to Maternal Heart Volume Weight of Infant and Duration of Pregnancy Mean Values*

Weight of Mother kg	<59.9	60 69.9	70≤
Maternal Heart Volume ml	532	593	677
Weight of Infant g	2553	2960	3247
Duration of Pregnancy days	263	268	268

In this table also the duration of pregnancy is about constant for the different groups but the maternal heart volume and the weight of the infant appear to be related to the weight of the mother

To decide in what way and to what extent the three factors – maternal heart volume maternal weight and duration of preg nancy – may influence the birth weight of the child the material has been subjected to a statistical analysis The purpose of this analysis is to state the functional association between the factors mentioned above and to determine whether any of these factors can serve as a predictor for the birth weight of the child As a

the heart volumes of mothers of premature and full-term infants, but as a whole our values are less than those described by Unnerus In about seventy per cent of the pregnancies resulting in premature infants, the heart volume of the mother was below 600 c c In the pregnancies resulting in full-term infants only about 50 per cent had a heart volume below 600 c c It is thus evident that the mothers of premature infants have a smaller heart volume than those of full term infants

Table I *Weight of Infant in Relation to Maternal Heart Volume, Weight of Mother and Duration of Pregnancy Mean Values*

Weight of Infant g	≤2500	>2500
Maternal Heart Volume ml	556	598
Weight of Mother, kg	59	64
Duration of Pregnancy, days	252	279

Table I shows the mean values for maternal heart volume, weight of the mother and duration of pregnancy for the two groups of infants It is apparent that the values for maternal heart volume and maternal weight and also for the duration of pregnancy are smaller in the premature group All these factors may of course *per se* influence the weight of the child

To eliminate the influence of pregnancy duration, the full term pregnancies (± 14 days) only were considered and the results are shown in Table II

Table II *Weight of Infant in Relation to Maternal Heart Volume and Weight of Mother Only Full-Term Pregnancies (280 ± 14 days) Mean Values*

Weight of Infant g	≤2500	>2500
Maternal Heart Volume, g	565	598
Weight of Mother, kg	59	64

Even so there is a difference concerning both heart volume and weight of mothers between premature and full term infants

In Table III the weight of the infant, the weight of the mother

and the duration of pregnancy is recorded for different groups of maternal heart volumes

Table III *Maternal Heart Volume in Relation to Weight of Infant Weight of Mother and Duration of Pregnancy Mean Values*

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result of earlier investigations (Räihä *et al*, 1956, Unnerus, 1959) it seems reasonable to presume that within the range of the factors examined the functional association is approximately linear We therefore describe and analyse the linear functional model for the association between the birthweight of the child and the above-mentioned factors

The regression equation used was of the type

$$\bar{y} = a + b(x_1 - \bar{x}_1) + c(x_2 - \bar{x}_2) - d(x_3 - \bar{x}_3)$$

$\bar{y}$ = the calculated average birth-weight of the child in g for *different values of the variables* x_1, x_2 and x_3

x_1 = weight of the mother in kg $\bar{x}_1$ = the average weight in the case-material

x_2 = maternal heart volume in c c $\bar{x}_2$ = the average heart volume in the case material

x_3 = pregnancy duration in days $\bar{x}_3$ = the average duration in the case-material

a, b, c and d are estimated parameters The three last mentioned are also called regression coefficients

The parameters are estimated in the usual way by means of the least square-method and the calculated regression function is

$$\bar{y} = 2808 - 13(x_1 - 62) - 1(x_2 - 578) - 21(x_3 - 265)$$

The regression coefficient for x_1, x_2 and x_3 differs significantly from zero and so all the factors are of some importance

In order to examine the exact importance in the regression model of the different factors the variations in the birth-weight of the child are used as a basis In the material examined the total variance for the birth weight was

$$s^2 = 616569$$

This variance may to a certain extent be explained by the fact that there is a functional association between the birth weight of the child and the factors examined and also to a great many factors not examined The existence of too many variables will result in unpredictable variations in the birth weight of the child Up to 50 per cent of the total variance may be explained by the factors studied above The remaining variation is caused by factors not studied here

It is evident that the pregnancy duration is of the greatest

Maternal Heart

We ght of Infant,g

000

10 kg – 130 g

000

2000

1000

40 50 60 70 80

We ght of Mothe kg

Fig 2 Relation of Weight of Infant to Weight of Mother Maternal Heart Volume and Duration of Pregnancy Constant

We ght of Infa t,g

4000

100 ml 100 g

3000

2000

1000

4 0 500 600 700 800

Maternal Heart Volume ml

Fig 3 Relation of Weight of Infant to Maternal Heart Volume Weight of Mother and Duration of Pregnancy Constant.

result of earlier investigations (Räihä *et al.*, 1956, Unnerus, 1959) it seems reasonable to presume that within the range of the factors examined the functional association is approximately linear. We therefore describe and analyse the linear functional model for the association between the birthweight of the child and the above-mentioned factors.

The regression equation used was of the type

$$\bar{y} = a + b(x_1 - \bar{x}_1) + c\,(x_2 - \bar{x}_2) - d(x_3 - \bar{x}_3)$$

$\bar{y}$ = the calculated average birth-weight of the child in g for *different values of the variables* x_1, x_2 *and* x_3

x_1 = weight of the mother in kg. $\bar{x}_1$ = the average weight in the case-material

x_2 = maternal heart volume in c.c. $\bar{x}_2$ = the average heart volume in the case-material

x_3 = pregnancy duration in days. $\bar{x}_3$ = the average duration in the case-material

a, b, c and d are estimated parameters. The three last mentioned are also called regression coefficients.

The parameters are estimated in the usual way by means of the least-square-method and the calculated regression function is

$$\bar{y} = 2808 - 13(x_1 - 62) - 1(x_2 - 578) - 21(x_3 - 265)$$

The regression coefficient for x_1, x_2 and x_3 differs significantly from zero and so all the factors are of some importance.

In order to examine the exact importance in the regression model of the different factors the variations in the birth weight of the child are used as a basis. In the material examined the total variance for the birth weight was

$$s^2 = 616569$$

This variance may to a certain extent be explained by the fact that there is a functional association between the birth weight of the child and the factors examined and also to a great many factors not examined. The existence of too many variables will result in *unpredictable* variations in the birth-weight of the child. Up to 50 per cent of the total variance may be explained by the factors studied above. The remaining variation is caused by factors not studied here.

It is evident that the pregnancy duration is of the greatest

Discussion

The present investigation started in order to confirm the en couraging results reported in a number of papers from the Women s Clinic in Helsingfors, (Räihä, Lind, Johansson, Kihlberg and Vara, 1956, Unnerus, 1959) These investiga tions were based on the fact that the total blood volume and the working capacity of the pregnant woman can be measured by the heart volume, since the blood volume and the heart volume, both under normal conditions and in normal pregnancy, are corre lated (Kjellberg Lönroth, Rudhe and Sjöstrand, 1950) It was later shown by Räihä et al (1956) that the frequency of premature births increases in women with small hearts and low hæmoglobin values In a later paper by Unnerus (1959) the methods of the investigation and the preliminary results were reported He showed that in about two thirds of the pregnancies resulting in premature delivery the heart volume of the mother was below 600 ml In the pregnancies resulting in full term deli veries on the other hand, only one third of the mothers had a heart volume below 600 ml There was good correlation between the weight of the baby and the maternal heart volume the day after parturition regardless of the duration of pregnancy

From Unnerus investigations it seemed evident that the heart volume of the mother is a factor which may influence the birth weight of the child By measuring the heart volume of pregnant women and by subjecting those with small hearts to special supervision we could thus have a possibility of preventing the birth of a premature child

The present investigation on the other hand clearly shows that neither the maternal heart volume nor the maternal weight can be used as a predictor for the prematurity of the child Ne vertheless we consider the relationship between maternal heart volume and prematurity worth further studies Even though the absolute value of the maternal heart volume cannot be used as a predictor for the birth weight of the child the *mode in which* the maternal heart responds to the strain of pregnancy may be of importance for the further progress of the pregnancy Thus pro- gramme is also being carried out at the Women s Clinic in Hel

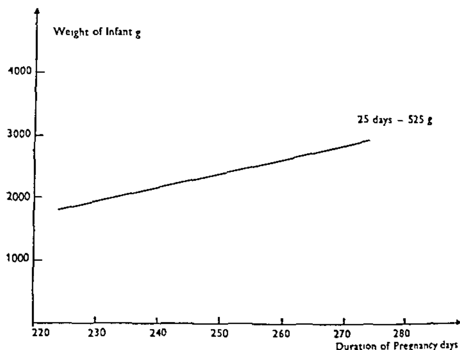


Fig 4 Relation of Weight of Infant to Duration of Pregnancy Maternal Heart Volume and Weight Constant

importance and this factor also causes more than 90 per cent of the explained variance The remaining variation may be explained by the maternal weight and heart volume

If one wants to make use of the functional association as a predictor it is of course not possible to use the duration of pregnancy So the regression equation may be

$$Y' = a + b'(X_1 - \bar{X}_1) + c'(X - \bar{X})$$

and after estimation of a, b' and c' we obtain

$$Y' = 2808 + 20(X_1 - 62) + (X - 578)$$

The regression coefficient for X does not significantly differ from zero (t 1,57), but this is the case for X_1 (t 3,33) The explained variance amounts to only 10 per cent of the total variance *The result of the statistical analysis is that neither maternal weight nor maternal heart volume is of practical value as a predictor for the prematurity of the child*

Discussion

The present investigation started in order to confirm the encouraging results reported in a number of papers from the Women's Clinic in Helsingfors, (Räihä Lind Johansson Kihlberg and Vara, 1956, Unnerus 1959) These investigations were based on the fact that the total blood volume and the working capacity of the pregnant woman can be measured by the heart volume, since the blood volume and the heart volume, both under normal conditions and in normal pregnancy, are correlated (Kjellberg, Lonroth, Rudhe and Sjostrand, 1950) It was later shown by Räihä *et al* (1956) that the frequency of premature births increases in women with small hearts and low hæmoglobin values In a later paper by Unnerus (1959) the methods of the investigation and the preliminary results were reported. He showed that in about two thirds of the pregnancies resulting in premature delivery the heart volume of the mother was below 600 ml In the pregnancies resulting in full term deliveries on the other hand only one third of the mothers had a heart volume below 600 ml There was good correlation between the weight of the baby and the maternal heart volume the day after parturition regardless of the duration of pregnancy

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singfors In co-operation with the pre-natal care centres of the city every pregnant woman is sent to the clinic and X ray examinations of her heart are performed at different stages of the pregnancy The preliminary results of this investigation are encouraging, but from a practical point of view it is very difficult to undertake such a close supervision of every pregnant woman including, *inter alia*, repeated X-ray examinations of her heart during the pregnancy

SUMMARY

The authors have studied the influence of maternal heart volume, maternal weight and pregnancy duration on the birth-weight of the child The maternal heart volume was determined roentgenologically two days after parturition The material consisted of 80 mothers of premature infants and 80 mothers of full-term infants The results were subjected to a statistical analysis The investigation has shown that neither the maternal heart volume nor the maternal weight can be used as a predictor for the birth-weight of the child

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CLINICAL ASSESSMENT OF HEART DISEASE DURING PREGNANCY

BY

BJORN BUEMANN AND EBBE KRAGELUND

Introduction

Recently, a number of clinical analyses of heart disease and pregnancy have been published in the Scandinavian literature, but these reports have dealt mainly with the problems concerning acquired heart disease

Our study is a continuation of the work of Tybjærg Hansen and Lachmann (1954) and comprises 184 patients with a total of 202 deliveries, 44 per cent in patients with congenital heart disease and 48 per cent in patients with acquired heart disease, including 9 per cent whose heart disease had been treated surgically The size of the series and distribution of the cases enabled us to carry out parallel investigations into the course of the pregnancy delivery and puerperium in patients with congenital acquired and surgically treated heart disease In particular, we tried to evaluate the changes in the functional capacity of the heart during the pregnancy and the incidence of cardiac and obstetrical complications

On the basis of comprehensive studies of the literature and experience from the Mount Sinai Hospital New York City Dack Bader and Bader in 1960 reviewed the problems arising when cardiac patients became pregnant

In normal women the pulse rate and the stroke volume increase to a maximum (+ 30 – 50 per cent) in the 7th–8th month. At the same juncture, there is a minor increase in red cell volume and a marked increase in plasma volume (+ 50 – 65 per cent). Before delivery, however, the pulse rate, stroke volume, and blood volume return almost to normal. During labour, a considerable oxygen deficiency occurs, resulting in an increase in oxygen uptake, pulse rate, and respiratory rate as well as systolic blood pressure. During the puerperium, on the other hand, there are no constant changes in cardiac function.

In patients with heart disease, the increase in the demands on the functional capacity of the heart during pregnancy and labour may result in an aggravation of the heart disease and, in rare cases (less than 1 per cent) in death. Cardiac decompensation and maternal death are most likely to occur in elderly multiparae with a long history of heart disease and a poor cardiac functional capacity. On the other hand, the incidence of decompensation and maternal mortality may be lowered by early and frequent medical supervision during the pregnancy.

Scandinavian authors have performed several studies on the incidence of heart disease in maternity departments, the relative incidence of congenital and acquired cases, the incidence of toxæmia, and of maternal mortality.

From Table I it is evident that deliveries in patients with heart disease make up from 0.23 per cent to 1.1 per cent of the total cases. In order to be able to compare the various series, we classified the heart diseases into groups of definitely congenital and definitely acquired ætiology as well as a separate group of cases of uncertain origin. This shows that the series comprised predominantly cases of acquired heart disease, from 38 per cent to 83.4 per cent, while congenital heart diseases were present in only from 9 per cent to 36 per cent.

A few authors have analysed the incidence of toxæmia. Bergman and Sjostedt (1954) found 7.6 per cent to 9.5 per cent in their series from Lund and Malmo respectively. Golden (1955) found a high incidence of toxæmia, 34.8 per cent. His criteria were albuminuria associated with a blood pressure exceeding 135 mm systolic and 90 mm diastolic. In statistical analyses,

Table I *Previous Scandinavian Analyses*

	Total No. of Deliveries	No. of Deliveries in Pts. with Heart Disease	Abortions, Spontaneous and Therapeutic	Incidence of Heart Disease	Nature of Heart Disease: Congenital	Nature of Heart Disease: Acquired	Nature of Heart Disease: Uncertain Origin	Incidence of Toxemia	Maternal Mortality
Bjerring 1935	9800	101	6	1.1 %		over 60 %	—	—	3.5 %
Bergman and Sjöstedt 1954	29101 / 37560	343	56	0.6 % / 0.6 %	9.3 %	83.4 %	7.1 %	7.6 % / 9.5 %	0 / 1.5 %
Tybjerg Hansen and Lachmann 1954	6900	62	0	0.9 %	36 %	38 %	26 %		3.6 %
Crona 1954	56652	145	56	0.36 %	9 %	71 %	19 %	—	1.5 %
Halmnäs and Nordström 1954	60000	137	12	0.23 %	22.6 %	58 %	10.7 %		0.8 %
Collén 1955	10324	44	0	0.4 %	28 %	59 %	12 %	34.9 %	10 %
Strand 1955	30492	87	0	0.29 %	14.9 %	79.3 %	6.8 %		2.3 %

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In patients with heart disease, the increase in the demands on the functional capacity of the heart during pregnancy and labour may result in an aggravation of the heart disease and, in rare cases (less than 1 per cent) in death. Cardiac decompensation and maternal death are most likely to occur in elderly multiparae with a long history of heart disease and a poor cardiac functional capacity. On the other hand, the incidence of decompensation and maternal mortality may be lowered by early and frequent medical supervision during the pregnancy.

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	37569			0 6 %				9 5 %	1 5 %
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Colden 1955	10324	44	0	0 4 %	28 %	59 %	12 %	34 8 %	10 %
Strand 1955	30482	87	0	0 28 %	14 9 %	78 1 %	6 8 %	—	2 3 %

Golden found a significantly increased incidence of toxaemia during pregnancy

The maternal mortality varied from 0 to 10 per cent

In addition, Westman (1945) analysed a 20-year series from several Swedish maternity departments Among 197,163 deliveries, he found 1,375 cases of heart disease, or 0 7 per cent

No detailed data are available regarding changes in the cardiac condition during the pregnancy, delivery, and puerperium. Bjerring (1925) reported that in 11 pregnancies (10 per cent) the cardiac function deteriorated to the extent of decompensation leading to 6 deaths In Strands (1955) series, decompensation occurred in 10 cases (11 5 per cent) Golden reported 3 cases of decompensation (6 4 per cent) during which all three patients went into spontaneous labour and gave birth to premature infants

In most of these reports, the classification of the cardiac status has been based on the criteria of the New York Heart Association, i e on clinical subjective criteria According to Robbe (1959) this clinical classification is not sufficiently accurate In 28 cases followed throughout pregnancy, delivery, and puerperium, she tried to assess the cardiac status by purely objective methods, mainly changes in the electrocardiograms, X-rays of the heart and phonocardiography, and extensive use of cardiac catheterization In addition, she followed the changes in basal oxygen consumption, total hæmoglobin, blood volume, heart volume, vital capacity, and alterations in physical working capacity In her series of 31 deliveries, the maternal mortality was nil, and toxæmia occurred in 2 cases (6 5 per cent)

Lastly, mention must be made of Werkos (1954) study on the physiological circulatory changes in normal pregnant women and in pregnant women with mitral disease His findings indicate that the increase in cardiac output during pregnancy is greater in patients with mitral disease than in normal patients This gives rise to a further increase in the pressure in the already impaired pulmonary circulation, leading to a tendency to frequent episodes of decompensation

Present Investigations

Material

The present material comprises all pregnant patients with heart disease admitted to the Royal Maternity Department B, Rigs hospitalet, Copenhagen, during the decade 1950–1959 (inclusive)

During this period the treatment of pregnant patients suffering from heart disease was centralized The assessment of the nature of the cardiac disease, the cardiac status, and treatment were under the supervision of the Cardiological Laboratory, Rigs hospitalet (A Tybjærg Hansen, M D), while concurrently the obstetrical treatment was carried out at Maternity Department B Here the principles of treating pregnant patients with heart disease were briefly as follows

1 Examination by cardiologist when first referred to the hospital
2 At home the patient should have as much help as possible in the domestic duties
3 Frequent measurement of weight and a low-salt diet.
4 Liberal admission to the Department, if needed and at least 4–5 weeks before calculated term
5 As far as possible, delivery at term Possible shortening of the second stage of labour
6 Bed rest for 14 days post partum During this period large doses of antibiotics were administered prophylactically

The series consists of 184 patients with a total of 202 deliveries during the period of the study and 39 patients who had thera peutic abortion because of their heart disease during the same period

Table II *Incidence of Heart Disease among the Pregnant Patients in Royal Maternity Department B*

	Total No. of Deliveries	No. of Deliveries in Patients with Heart Disease
1950–1954 (incl.)	10074	89 (0 9 %)
1955–1959 (incl)	12219	113 (0 9 %)

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	Total No. of Deliveries	No of Deliveries in Patients with Heart Disease
1950–1954 (incl.)	10074	80 (0 9 %)
1955–1959 (incl)	12219	113 (0 9 %)

Table II gives the *number and percentage* of patients with heart disease admitted to Department B The series is divided into two 5-year periods, and it is apparent from the table that no changes in the frequency of deliveries took place within these two periods Although it is endeavoured to centralize the treatment of pregnant patients with heart disease in Greater Copenhagen at Rigshospitalet, the incidence cannot be converted to apply to the general population, partly because there have no doubt been cases of undiagnosed heart disease, and partly because the decision to perform therapeutic abortion on account of heart disease is made also in other hospitals

Type of Heart Disease

The distribution by type of heart disease is set out in Table III This shows a very high proportion of congenital cases, *viz* 44 per cent (including the operated cases) Accordingly, the material is suitable for assessment of the course of pregnancy in these patients The small group C is kept separate, because in regard to the course of pregnancy, delivery, and puerperium it corresponds to the group of congenital cases, although ætiologically it rather belongs to the group of acquired heart disease The table also gives the number of therapeutic abortions performed in the Department during the same period (16 per cent *of the total pregnancies)* The *distribution of these patients in* the individual types of disease corresponds to the distribution of deliveries apart from the fact that a relatively large number of patients with surgically treated heart disease were subjected to therapeutic abortion

Age and Parity

Fig 1 gives the age distribution of the patients with congenital and with acquired heart disease (including surgically treated cases) It is seen that the largest age group among the congenital cases is 21–25 years *In the group of acquired heart disease the* number of older patients (over 30) is far greater In the latter group 38 per cent were over 30 years of age as compared with only 12 per cent of the congenital cases

Table III *Patients with Heart Disease Delivered in Royal Maternity Department B*

	1950 1959 (incl.)	No of Deliveries 1950–1959 (incl)	No of Patients Having Therapeutic Abortion 1950 1959 (incl.)
Congenital heart disease			
Coarctation of the aorta	6	7	1
Patent ductus arteriosus	5	7	0
Isolated pulmonary stenosis	17	22	1
Ventricular septal defect	13	13	4
Atrial septal defect	9	10	1
Tetralogy of Steno-Fallot	3	3	3
Aortic valve disease	5	5	0
Mitral disease	1	2	1
Type uncertain	7	8	0
Total	66	77 (38 %)	11
Acquired heart disease			
Mitral stenosis	34	35	6
Mitral insufficiency	10	11	2
Mitral stenosis + insufficiency	15	18	3
Aortic valve disease	6	8	1
Mitral + aortic valve disease	9	9	0
Chronic cor pulmonale	2	2	0
Type uncertain	7	7	2
Total	83	90 (45 %)	14
Group C			
Paroxysmal tachycardia	7	7	1
Extrasystoles	3	3	1
Heart block without other heart disease	7	7	0
Total	17	17 (8 %)	2
Group D Heart disease treated surgically			
Congenital			
Coarctation of the aorta	2	2	0
Patent ductus arteriosus	7	7	1
Isolated pulmonary stenosis	1	1	0
Atrial septal defect	0	0	2
Tetralogy of Steno-Fallot	2	2	1
Total	12	12 (6 %)	4
Acquired			
Mitral stenosis	5	5	8
Mitral stenosis + insufficiency	1	1	0
Total	6	6 (3 %)	8
Entire Seri	0		

Table II gives the *number and percentage* of patients with heart disease admitted to Department B. The series is divided into two 5-year periods, and it is apparent from the table that no changes in the frequency of deliveries took place within these two periods. Although it is endeavoured to centralize the treatment of pregnant patients with heart disease in Greater Copenhagen at Rigshospitalet, the incidence cannot be converted to apply to the general population, partly because there have no doubt been cases of undiagnosed heart disease, and partly because the decision to perform therapeutic abortion on account of heart disease is made also in other hospitals.

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Age and Parity

Fig. 1 gives the age distribution of the patients with congenital and with acquired heart disease (including surgically treated cases). It is seen that the largest age group among the congenital cases is 21–25 years. In the group of acquired heart disease the number of older patients (over 30) is far greater. In the latter group 38 per cent were over 30 years of age as compared with only 12 per cent of the congenital cases.

Class III Gross limitation of activity Discomfort on less than ordinary activity

Class IV Discomfort on any sort of physical activity Symptoms of cardiac decompensation at rest

Neither before the pregnancy nor later during the pregnancy and puerperium, could we supplement the analysis by serial electrocardiograms and X rays of the heart, partly because these studies were carried out at different stages of the pregnancy and puerperium and partly because they were not performed in all the cases It must be pointed out, therefore, that our assessment must be liable to error, because the classification of the patients by functional capacity is based on the subjective estimate of the patients as well as the authors In a retrospective study, however, no other classification is possible

Table IV *Functional Capacity of the Heart Distribution Prior to Present Pregnancy*

Class	I	II	III	IV
Patients with congenital heart disease	53 (69 %)	23 (30 %)	1 (1 %)	0
Patients with acquired heart disease	52 (58 %)	36 (40 %)	2 (2 %)	0
Patients of Group C	13	3	1	0
Patients with heart disease treated surgically	13	4	1	0
Entire Series	131 (65 %)	66 (33 %)	5 (2 %)	0
Patients who had therapeutic abortion	7 (18 %)	31 (79 %)	1 (3 %)	0

Table IV gives the distribution into groups of cardiac functional capacity up to the time of the present pregnancy It is evident from this table that 65 per cent of our patients had not experienced any symptoms prior to the pregnancy while 42 per cent of the acquired and 31 per cent of the congenital cases had symptoms before the pregnancy Only a few were in Class III and none in Class IV Furthermore the table gives the distri

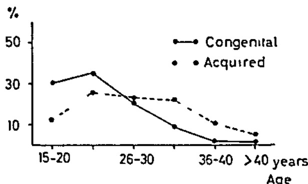


Fig 1 Number of deliveries Distribution of maternal age

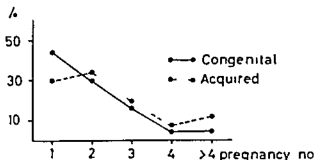


Fig 2 Number of deliveries Distribution by number of pregnancy

The distribution by parity is given in Fig 2, which also shows the two groups of congenital and acquired heart disease (including the surgically treated cases) It is seen that the patients were predominantly primi- and secundi-gravidæ Only 25 per cent of the patients with congenital and 36 per cent of those with acquired heart disease were Gravidæ III or over

Pre pregnancy Functional Capacity of the Heart

The functional capacity of the heart up to the time of the pregnancy was assessed on the basis of the history in accordance with the classification of the New York Heart Association

Class I No limitation of activity or discomfort on ordinary activity

Class II Slight limitation of activity and some discomfort on ordinary activity

proportion of the patients moved to a poorer class Among the congenital cases 5 out of 13 patients with ventricular septal defect and 2 out of 3 patients with the tetralogy of Steno-Fallot deteriorated to a poorer group Among the acquired cases 11 out of 18 patients with mitral stenosis combined with mitral insufficiency changed to a poorer group

Conversely, we found a more favourable course in patients who had been subjected to cardiac surgery, 15 out of 18 remaining in their pre pregnancy class

In this connection it may be mentioned also that 36 per cent (14/39) of the patients who had therapeutic abortions moved to a functional class poorer than before their pregnancy

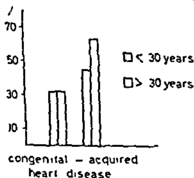


Fig 4 Alteration in functional capacity of heart during pregnancy
Dependence on age

In Fig 4 the change in functional capacity of the heart in the course of pregnancy is related to age This shows that deterioration is most common in patients over 30 years of age with acquired heart disease

Similarly the functional capacity of the heart during pregnancy was related to the number of the pregnancy (Fig 5) and in both the congenital and acquired groups deterioration was found to be common, among patients pregnant for more than the second time

bution by the pre-pregnancy functional capacity of the heart, for the patients who had therapeutic abortion The great majority of this group had exhibited cardiac symptoms before the pregnancy (82 per cent) However, only one had to be assigned to Class III and none to Class IV

Cardiac Status during Pregnancy, Delivery, and Puerperium

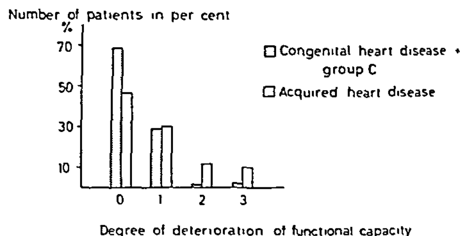


Fig 3 Alterations in functional capacity of the heart during pregnancy

Fig 3 shows how many patients remained in the same class or deteriorated to a poorer class in the course of pregnancy Since, as already mentioned, the course in Group C (*cf* Table II) accorded predominantly with the course in the congenital heart diseases, these two groups are considered together It is *evident that 69 per cent of the congenital cases remained in* the class to which they had been assigned prior to pregnancy Among the patients with acquired heart disease, on the other hand, only 47 per cent *remained in their original class*, while 53 per cent changed to a poorer class Whereas the patients with congenital heart disease who did deteriorate during the pregnancy moved in most cases only to the next class, 22 per cent of the patients with acquired heart disease deteriorated to a class 2 or 3 grades worse than their pre-pregnancy class

In a few of the sub-groups (*cf* Table II), a particularly large

perium, since the patients are then mainly confined to bed and in a hospital environment During this period we tried to assess the cardiac status by means of the following signs Orthopnoea, cyanosis (periodical or constant) and tachycardia (maximum pulse rate exceeding 100/min) One or more of these signs during labour and puerperium were taken to indicate reduced functional capacity of the heart

Table V *No of Patients Who Developed Orthopnoea Cyanosis or Tachycardia during Labour or Puerperium*

	During labour	During the Puerperium
Congenital heart disease + Group C	23 (24 %)	15 (16 %)
Acquired heart disease	22 (24 %)	19 (21 %)
Heart disease treated surgically	3	5
Entire series	48 (24 %)	39 (19 %)

Table V lists the incidence of these cardiac signs in the various groups of patients during labour and during the puerperium up to the day of discharge It is evident that cardiac signs appeared during labour in about 25 per cent and during the puerperium in about 20 per cent of the patients In this respect there was no difference between patients with congenital and patients with acquired heart disease It must be mentioned that the named signs were often mild and transient

Out of the 48 patients who developed cardiac signs during labour 18 also had such signs during the puerperium In the remaining 21 patients showing cardiac signs during the puerperium no such signs had been present at the time of delivery

In Fig 7 the incidence of these cardiac signs during labour and puerperium is plotted against alterations in the functional capacity of the heart during pregnancy The histograms show that cardiac signs during labour and the puerperium were most common in patients whose functional capacity had deteriorated during the course of pregnancy

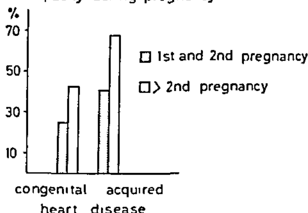


Fig 5 Alteration in functional capacity of heart during pregnancy Dependence on number of pregnancy

Lastly, deterioration of the functional capacity of the heart during pregnancy was related to the pre pregnancy functional ability (*Fig 6*) *Such deterioration was of practically equal fre* quency whether the patients belonged to Class I, II, or III, as all the patients were exposed to the same stress

While the functional capacity of the heart may be assessed before and during the pregnancy on the basis of information supplied by the patients, this cannot be done during labour and puer

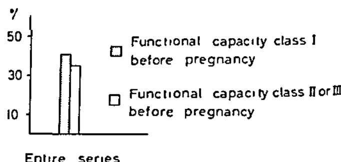


Fig 6 Alteration in functional capacity of heart during pregnancy Dependence on pre pregnancy functional capacity

perium, since the patients are then mainly confined to bed and in a hospital environment During this period we tried to assess the cardiac status by means of the following signs Orthopnoea, cyanosis (periodical or constant) and tachycardia (maximum pulse rate exceeding 100/min) One or more of these signs during labour and puerperium were taken to indicate reduced functional capacity of the heart

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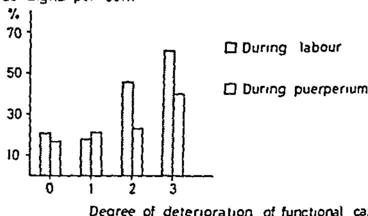


Fig 7 Incidence of cardiac signs in relation to functional capacity of heart during pregnancy

In addition, we assessed the cardiac function on the basis of the frequency with which it had been found necessary to institute cardiac therapy in the Department

Table VI *Digitalization and Dehydration among Patients with Heart Disease*

	Digitalization			Dehydration		
	During Pregnancy	During Labour	During the Puerperium	During Pregnancy	During Labour	During the Puerperium
Congenital heart disease + Group C	6 (6%)	2 (2%)	4 (4%)	11 (12%)	0	1 (1%)
Acquired heart disease	24 (26%)	16 (18%)	21 (23%)	18 (20%)	1 (1%)	2 (2%)
Heart disease treated surgically	2	2	3	3	0	0
Entire series	32 (16%)	20 (10%)	28 (14%)	32 (16%)	1	3 (1%)

According to the table, it was predominantly among the patients with acquired heart disease that the cardiac signs were so serious as to necessitate dehydration and/or digitalization

Incidence of Complications before Pregnancy, and during Pregnancy, Labour, and Puerperium

The complications are listed on the basis of the history and data in the case records as follows

Cardiac complications

- Atrial fibrillation
- Thrombosis and embolism
- Acute rheumatic myocarditis
- Bacterial endocarditis

Pulmonary complications

- Bronchitis
- Pneumonia
- Hæmoptysis
- Pulmonary œdema

Infectious complications

- Pyrexia (exceeding 38°C) for more than 24 hours
- Pyelitis – pyelonephritis

Arterial hypertension and/or albuminuria

(the criteria of arterial hypertension before and during the pregnancy being $>$ 140 mm Hg systolic and during labour $>$ 150 mm Hg systolic)

Jaundice

Hydramnios

Death

Table VII *Incidence of Complications in Pregnant Patients with Heart Disease*

	Before Pregnancy	During Pregnancy	During Pregnancy Labour and the Puerperium Total
Congenital heart disease + Group C	12 (13%)	22 (23%)	45 (49%)
Acquired heart disease	13 (14%)	44 (48%)	60 (66%)
Heart disease treated surgically	1	9	14
Entire series	26 (13%)	75 (37%)	120 (59%)

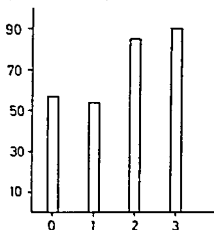


Fig 8 Incidence of complications in relation to alteration in functional capacity during pregnancy

Table VII gives the incidence of these complications before and during the pregnancy It lists also the total number of patients who developed one or more of these complications during pregnancy, labour, or the puerperium According to the table, a total of 59 per cent of the patients developed one or more complications at some stage of the pregnancy, labour, or the puerperium In a total of 37 per cent the complications were present during the pregnancy The incidence of complications is far higher in patients with acquired than with congenital heart disease In the subgroups (*cf* Table II), the number of patients developing complications is approximately equally distributed apart from the fact that all the patients with coarctation of the aorta had arterial hypertension Out of the 26 patients with pre-pregnancy complications, 20 also developed complications during the pregnancy

In Fig 8 the total incidence of complications during pregnancy, labour, and the puerperium is plotted against the alterations in the functional capacity of the heart during the pregnancy It is seen that complications were most common in patients who were reduced to a class of cardiac functional capacity which was 2 or 3 grades worse than that to which they had belonged before

pregnancy Nearly all of these patients developed complications But even the patients whose functional capacity did not alter during the pregnancy or only moved down to a class one grade worse than the pre pregnancy class showed an incidence of complications of just over 50 per cent

Table VIII *Complications during Pregnancy Labour and the Puerperium among Patients with Heart Disease*

	Cardiac	Pulmonary	Infectious	Hypertension + Albuminuria	Jaundice	Hydramnios	Death
Congenital heart disease + Group C	6 (6%)	1 (1%)	5 (5%)	36 (38%)	0	0	1 (1%)
Acquired heart disease	14 (15%)	26 (29%)	16 (18%)	31 (34%)	4 (4%)	2 (2%)	2 (2%)
Heart disease treated surgically	0	3	7	6	0	1	0
Entire series	20 (10%)	30 (15%)	28 (14%)	73 (36%)	4 (2%)	3 (1%)	3 (1 5%)

Table VIII gives the incidence of the individual complications during the entire period of the pregnancy labour and the puerperium (up to the day of discharge) It lists also the total number of complications in patients who developed several complications belonging to the different groups (*cf* page 15)

Cardiac complications occurred predominantly in patients with acquired heart disease Out of the 20 cardiac complications 13 were a trial fibrillation In 10 cases fibrillation set in during the pregnancy in 2 during labour and in one during the puerperium In 10 of these 13 patients worsening of the functional capacity occurred during the pregnancy It is worth emphasizing that the 18 surgically treated cases had no cardiac complications at all

Pulmonary complications and jaundice interpretable chiefly as signs of venous congestion were observed almost solely in patients with acquired heart disease

The incidence of infection was higher in patients with acquired heart disease

Arterial hypertension and/or albuminuria were the mon complications, both in congenital and in acquire equally common in the two groups It is difficult to high incidence (36 per cent) of these complications pointed out that out of the total of 73 patients who albuminuria and/or hypertension, 17 had albuminur associated hypertension It seems most reasonable to a in the majority of these cases the condition was not in as pre-eclampsia, but as a complication related to v gestion In the tabular survey (page 17) we also coun tension in coarctation of the aorta as a complication of the 9 patients with coarctation of the aorta had hy without attendant albuminuria Even if the rate of co for these two groups (a total of 24 patients) is ded probable frequency of pre-eclampsia in heart disease is increased, viz a total of 24 per cent

Owing to this high incidence of hypertension and/o uria in patients with heart disease, we investigated w presence of these two complications was correlated w complications

Table IX *Correlation between Hypertension Albuminuria and C plications in Pregnant Patients with Heart Disease*

	Total patients	Patients with Cardiac Compli cations	Disper Inde
Patients with hyper tension albuminuria	73	12 (16 %)	5 6
Other patients	129	8 (6 %)	

It is apparent from Table IX that such a correlation Cardiac complications were almost 3 times as common who had developed hypertension and/or albuminuria pregnancy, labour, or the puerperium as among the o dispersion index was calculated according to the form

$$\frac{[(A \times D) - (B \times C)]^2 \times (A + B + C + D)}{(A + B) \times (C + D) \times (A + C) \times (B + D)}$$

(Fischer, 1954), and was found to be 5 6, or 2 4 times the standard error

The maternal mortality was 1 5 per cent three patients having died Their case reports are given below

Case Reports

(1) Case rec 1173/50 Gravida II Para I aged 31 Rheumatic fever allegedly without cardiac complications at the age of 6 Since then she had been symptom free (functional class I) until the present pregnancy when she developed severe cardiac symptoms i e constant cyanosis of the lips and increasing dyspnœa on exertion (functional class III) The patient was admitted 5 weeks before calculated term in a state of severe dyspnœa and cyanosis An electrocardiogram showed a considerable right sided prepon derance

The bag of waters had ruptured in her home immediately before admission and an hour later she went into labour During the subsequent hours the patient became increasingly debilitated showing marked cardiac decom pensation Treatment with strophantin was instituted Seven hours after admission she was delivered of an asphyxiated infant of 1400 g which pre sented by the breech During the entire course of labour the patient had been extremely dyspnoeic and cyanosed After the spontaneous delivery of the placenta she deteriorated further her respirations became irregular and she died half an hour post partum

Post mortem diagnosis Severe chronic cor pulmonale

Histological diagnosis Primary arteriosclerosis of the pulmonary artery (Ayerza s disease) Arteriosclerosis of the pulmonary artery congestion and œdema of the lungs (Cf also Fuchs 1953)

(2) Case rec 355/52 Gravida II Para I aged 24 Heart trouble from childhood but had taken part in physical exercises and other forms of sport At the age of 18 spontaneous abortion in the 4th month During the first pregnancy increasing cardiac symptoms necessitating administration of digitalis for some time Since then no specific cardiac therapy (functional class I) During the next pregnancy she again developed cardiac symptoms ri dyspnœa palpitations and œdema (functional class IV) Digi talis therapy was started again The pulse was irregular of the perpetual arrhythmia type ECG showed atrial fibrillation, and chest radiagraphy a greatly dilated heart presumably due to mitral valve disease Admitted 5 weeks before calculated term, the patient was delivered of a live infant weighing 2450 g about 10 days before term In order to avoid unnecessary strain on the heart during the second stage of labour the patient was deliv

Arterial hypertension and/or albuminuria were the most common complications, both in congenital and in acquired cases, and equally common in the two groups It is difficult to explain the high incidence (36 per cent) of these complications It may be pointed out that out of the total of 73 patients who developed albuminuria and/or hypertension, 17 had albuminuria without associated hypertension It seems most reasonable to assume that in the majority of these cases the condition was not interpretable as pre-eclampsia, but as a complication related to venous congestion In the tabular survey (page 17) we also counted hypertension in coarctation of the aorta as a complication Seven out of the 9 patients with coarctation of the aorta had hypertension without attendant albuminuria Even if the rate of complications for these two groups (a total of 24 patients) is deducted, the probable frequency of pre-eclampsia in heart disease is still greatly increased, viz a total of 24 per cent

Owing to this high incidence of hypertension and/or albuminuria in patients with heart disease, we investigated whether the presence of these two complications was correlated with cardiac complications

Table IX *Correlation between Hypertension Albuminuria and Cardiac Complications in Pregnant Patients with Heart Disease*

	Total patients	Patients with Cardiac Complications	Dispersion Index
Patients with hypertension albuminuria	73	12 (16 %)	5 6
Other patients	129	8 (6 %)	

It is apparent from Table IX that such a correlation was found Cardiac complications were almost 3 times as common in patients who had developed hypertension and/or albuminuria during the pregnancy, labour, or the puerperium as among the others The dispersion index was calculated according to the formula

Out of the entire series, operative delivery was indicated in 31 per cent, in the great majority by the vaginal route (by forceps or vacuum extractor) Cæsarean section was carried out in 4 cases indicated in 3 by purely obstetric factors Out of the 59 forceps and vacuum extractor deliveries, 25 were for purely obstetric causes Only 35 (18 per cent) of the patients were delivered instrumentally because of their heart disease It was a principle in the Department to let patients with heart disease go to term and to shorten the second stage of labour, if it did not prove very easy Table V, however, shows that the incidence of cardiac signs during labour was higher than the incidence of obstetrical interventions indicated by the heart disease Thus, in a number of the patients the delivery was spontaneous even though cardiac signs appeared in the course of labour Consequently, instrumental delivery probably ought to have been employed somewhat oftener

The table also gives the number of patients with a blood loss exceeding 500 ml in the course of delivery of the infant and the placenta The high incidence of greater blood loss (10 per cent) can be naturally related to the high incidence of operative obstetrics

Summary and Conclusions

During the decade 1950–1959 a total of 184 patients suffering from heart disease were delivered of 202 infants in the Royal Maternity Department B Rigshospitalet Copenhagen On the basis of the clinical course of pregnancy labour and puerperium, the following items may be stressed

1 38 per cent of the patients had congenital and 45 per cent acquired heart disease 9 per cent had been subjected to operation for their heart disease

2 There was a preponderance of older (> 30 years) patients and of multigravidæ among the patients with acquired heart disease

3 During the pregnancy the functional capacity of the heart deteriorated in 31 per cent of the patients with congenital and in 47 per cent of those with acquired heart disease especially in older multigravidæ with acquired heart disease

ered by low forceps The delivery was uncomplicated, and did not cause deterioration of the cardiac status During the puerperium the patient showed increasing pyrexia, up to a maximum of 39 5°C, which could not be definiteley explained Since the condition proved refractory to high doses of antibiotics and digitalis, the patient was transferred, 16 days post partum, to Medical Department B, where she died 3 days later

Diagnosis Rheumatic heart disease (stenosis and insufficiency of the mitral valve, stenosis of the aorta, stenosis and insufficiency of the tricuspid valve)

(3) Case rec 111/59 Gravida III, Para II aged 32 with congenital heart disease which had been clinically assigned to the Eisenmenger type (functional class II) In addition, severe kyphoscoliosis and pes equino-varus During her last pregnancy the patient had been in a fairly good condition apart from accentuation of dyspnœa and frequent attacks of palpitations (functional class III) Admitted 4 weeks before calculated term after rupture of the bag of waters and onset of labour Ten minutes after admission, she gave birth to a live infant weighing 1400 g Apart from cyanosis, the patient had been unaffected by the labour The puerperium was also uneventful Eight days after delivery the patient discharged herself Three days later she was found dead in her home Legal autpsy, Congenital malformation of the heart (ventricular septal defect, atrial septal defect, patent ductus arteriosus, and chronic cor pulmonale)

Obstetric Interventions

Table X *Obstetric Interventions on Patients with Heart Disease*

	Total Patients	Operative Vaginal Delivery	Cæsarean Section	Loss of Blood during Delivery > 500 ml
Induced labour	36	14 (39%)	1 (3%)	
Spontaneous delivery	166	45 (27%)	3 (2%)	
Entire series	202	59 (29%)	4 (2%)	21 (10%)

Table X gives a survey of the obstetric operations performed on our patients with heart disease Therapeutic induction of labour comprised drug induction with or without rupture of the membranes It must be pointed out that the majority of these operations were carried out for indications other than the heart disease (toxæmia, postmaturity) Where the heart disease was the only indication, all the patients but one were at term or slightly past term

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4 Among the patients with congenital heart disease, deterioration during pregnancy was most common in the presence of ventricular septal defect and the tetralogy of Steno-Fallot. Among the patients with acquired heart disease deterioration was most apt to occur in cases of mitral stenosis combined with mitral insufficiency

5 During delivery a total of 24 per cent and during the puerperium a total of 19 per cent developed cardiac signs (exertional dyspnoea, cyanosis, tachycardia) These signs were observed particularly in patients whose cardiac functional capacity deteriorated in the course of pregnancy

6 The total incidence of complications during the entire course of pregnancy, delivery, and the puerperium was 49 per cent in patients with congenital and 66 per cent in patients with acquired heart disease Complications occurred particularly in patients whose cardiac functional capacity deteriorated during the pregnancy

7 Among the complications, toxæmia (hypertension and/or albuminuria) was most common (24 per cent), and was equally common in cases of acquired and congenital heart disease There was a correlation between the incidence of cardiac complications and hypertension and/or albuminuria

8 Cardiac complications occurred in 10 per cent and pulmonary complications in 15 per cent, predominantly in patients with acquired heart disease

9 The incidence of operative obstetrics was 31 per cent indicated in 18 per cent by the heart disease alone

10 The maternal mortality was 1 5 per cent

11 The series includes 18 patients whose heart disease had been treated surgically This group is too small to permit general conclusions, but it may be pointed out that these patients fared well Only 3 of them moved to a poorer functional class in the course of pregnancy, the incidence of cardio pulmonary complications was low, and aggravation of the cardiac status during labour was rare (3/18)

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MORBIDITY AND MORTALITY AMONG INFANTS BORN TO MOTHERS WITH HEART DISEASE

BY

BJORN BUEMANN AND EBBE KRAGELUND

Introduction

In this study we have tried to evaluate the incidence of congenital malformations, asphyxia neonatorum and prematurity in infants born to mothers with heart disease

A number of clinical analyses on heart disease and pregnancy have recently been published in the Scandinavian literature These reports have mainly dealt with patients suffering from acquired heart disease Our study comprises 184 patients with a total of 202 deliveries Forty four per cent of the cases had certain congenital heart disease and forty-eight per cent acquired heart disease, including nine per cent whose heart disease had been treated surgically Therefore we were able to carry out parallel investigations into the incidence of congenital malformations, asphyxia neonatorum and prematurity

In the Scandinavian literature no detailed data are available regarding the incidence of congenital malformations and asphyxia neonatorum The incidence of prematurity was increased in several series, to a maximum of 16 7 per cent (Malmnäs and Nordstrom, 1954) Golden (1955) found a statistically significant lower birth weight among infants born to mothers with acquired heart disease (Table I)

Table I *Previous Scandinavian Analyses*

	No of Deliveries in Pts. with Heart Disease	Incidence of Prematurity	
Bjerring (1925)	101	8 %	
Bergman &		6 2	Lund
Sjöstedt (1954)	343	12 6	Malmo
Crona (1954)	145	5 5	
Malmnas &			
Nordstrom (1954)	137	16 7	
Golden (1955)	44	6 9	
Strand (1955)	87	8 1	
Robbe (1959)	31	16 1	

Present Investigation

The present series comprises all infants born to patients with heart disease admitted to the Royal Maternity Department B, Rigshospitalet, Copenhagen, during the decade 1950–1959 (incl), a total of 202 infants Regarding the distribution of the mothers by age parity type of heart disease, and regarding the obstetrical procedures we refer to our previous study on pregnancy and heart disease (Buemann and Kragelund 1962)

Table II *Incidence of Congenital Malformations Asphyxia Neonatorum and Prematurity among the Infants of Mothers Suffering from Heart Disease*

Maternal Condition	No of Infants	Congenital Malformations	Asphyxia Neonatorum	Prematurity
Congenital heart disease	94	4 (4%)	2 (2%)	8 (9%)
Acquired heart disease	90	3 (3%)	7 (8%)	23 (25%)
Operated heart disease	18	0	0	2
Entire Series	202	7 (3%)	9 (4%)	33 (17%)

Table II lists the incidence of congenital malformations asphyxia neonatorum and prematurity Congenital malformations were relatively common and occurred in a total of 7 infants (2 cases of mongolism one of hydrocephalus 2 of congenital heart disease one of hypospadias and one of an accessory digit) The babies

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A number of clinical analyses on heart disease and pregnancy have recently been published in the Scandinavian literature These reports have mainly dealt with patients suffering from acquired heart disease Our study comprises 184 patients with a total of 202 deliveries Forty-four per cent of the cases had certain congenital heart disease and forty-eight per cent acquired heart disease, including nine per cent whose heart disease had been treated surgically Therefore, we were able to carry out parallel investigations into the incidence of congenital malformations, asphyxia neonatorum and prematurity

In the Scandinavian literature no detailed data are available regarding the incidence of congenital malformations and asphyxia neonatorum The incidence of prematurity was increased in several series, to a maximum of 16 7 per cent (Malmnäs and Nordstrom, 1954) Golden (1955) found a statistically significant lower birth weight among infants born to mothers with acquired heart disease (Table I)

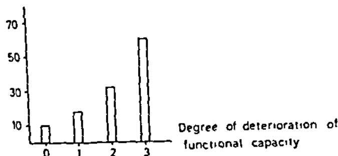


Fig 2 Dependence of prematurity upon functional capacity of heart during pregnancy

Thirty three infants weighed less than 2 500 g, being of an average gestational age of 29 9–33 9 weeks It must be assumed, therefore that there was both a high incidence of prematurity and a low birth weight in relation to gestational age This appears to confirm Räihä s *et al* (1956, 1957) theories on the circulatory stress tending to a birth weight lower than that which corresponds to the calculated gestational age It may be mentioned however that among the 33 cases of prematurity labour was induced in 5 cases (in three because of toxæmia in one because of intrauterine death, and in one because of cardiac decompensation complicated by pulmonary infarction)

In Fig 2 the incidence of prematurity is related to the alterations in the functional capacity of the maternal heart during pregnancy The functional capacity of the heart before and during pregnancy was assessed on the basis of the history in 4 classes in accordance with the classification of the New York Heart Association Evidently the tendency to bear premature infants increased with the degree of decompensation which occurred during pregnancy and reached a maximum of sixty per cent in those patients whose functional capacity deteriorated from class 1 to class 4 Among patients whose functional capacity did not alter during pregnancy the incidence of prematurity was only 11 per cent

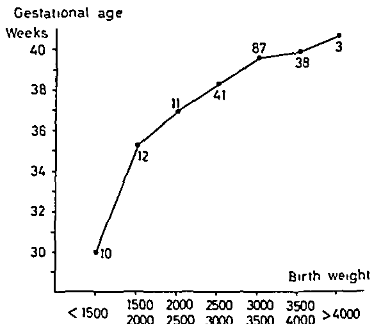


Fig 1 Relation between birth weight and gestational age among infants born to mothers with heart disease

with congenital heart disease were born to mothers also suffering from congenital heart disease In this connection it must be borne in mind that the diagnosis of congenital heart disease is extremely difficult during the neonatal period Consequently, the stated incidence must be considered a minimum value

Neonatal asphyxia seldom occurred (4 per cent)

On the other hand, prematurity, defined as a birth weight under 2500 g, was very common, particularly in the group of mothers with acquired heart disease in which the incidence was 25 per cent To ascertain whether this was the result of prematurity or whether the birth weight was merely low in relation to the gestational age the graph shown in Fig 1 was constructed

This figure records the relation between gestational age and birth weight The gestational age was calculated from the possibly unreliable record of the first day of the last menstrual period The figures on the curve give the total number of babies in each weight group It is seen that 128 infants weighed more then 3,000 g and that their average gestational age was 39 6–40 7 weeks

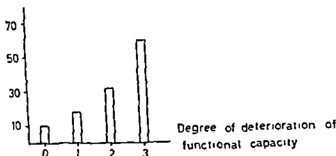


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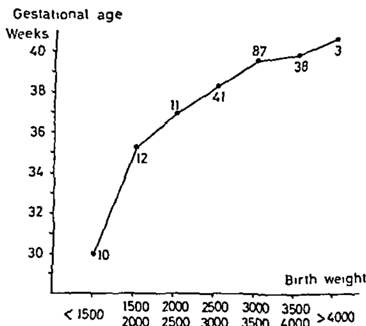


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5 The infant mortality rate was a total of 8 per cent (3 per cent among infants born to mothers with congenital and 12 per cent among infants born to mothers with acquired heart disease) The stillbirth rate was 3 per cent, and the mortality among the mature infants was 2 per cent

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Table III *Perinatal Mortality among Infants of Mothers Suffering from Heart Disease*

Maternal Condition	No of Infants	Perinatal Mortality	Stillborn	Mortality among Mature Infants
Congenital heart disease	94	3 (3 %)	0	0
Acquired heart disease	90	11 (12 %)	3 (3 %)	2 (3 %)
Operated heart disease	18	2	2	1
Entire Series	202	16 (8 %)	5 (3 %)	3 (2 %)

Lastly, Table III gives the perinatal mortality up to the time of discharge from the Department It is seen that the perinatal mortality was high (8 per cent) in the total series and particularly high (12 per cent) among the infants of mothers suffering from acquired heart disease This mortality must be viewed in the light of the large number of premature (Table II) and still born babies in this group Among the mature infants alone the total mortality was 2 per cent, but in this group, too, the deaths occurred predominantly among babies born to mothers with acquired heart disease

Summary and Conclusions

During the decade 1950–1959 a total of 202 infants were born to 184 mothers suffering from heart disease in the Royal Maternity Department B, Rigshospitalet, Copenhagen Regarding the morbidity and perinatal mortality among these babies the following items may be stressed

1 Congenital malformations were present in 3 per cent of the infants
2 Asphyxia neonatorum was rare (4 per cent)
3 The total incidence of prematurity was 17 per cent (9 per cent among infants born to mothers with congenital heart disease and 25 per cent among those born to mothers with acquired heart disease)
4 Prematurity occurred predominantly in cases where the maternal heart disease was associated with functional deterioration during the pregnancy

The rupture occurs in about 77 per cent of cases in the third on the fœtal side, in 9 per cent in the third on the placental side and in the remainder in the middle third The prognosis for the infant is poorer the earlier the rupture occurs

The majority of the ruptures of the cord occur *post partum* A special group consists of ruptures of intrauterine intrapartum occurrence (e g Bloxsome, 1914, Vermelin, 1924, Siddal, 1925, Sackett, 1934) Even rarer are ruptures of the umbilical cord which occur before the onset of labour pains, *i e* ante-partum of which the present authors have found only one report in the literature (Silbernagel and Fidler, 1942) However, as the present case differs from that one in many respects, the following report may be of interest

Case Report

The patient was a para III 28 years of age Her two earlier pregnancies had progressed normally However in both of the deliveries the second stage of labour had been prolonged somewhat by the relatively small pelvis (conjugata vera 10 6 cm.) in consequence of which the younger of the infants especially was notably asphyxiated but was resuscitated (the birth weights 1956 3 400 g and 1958 3 700 g) From the experience gained in the second delivery a Cæsarean section was planned in the event of a subsequent pregnancy continuing to term

The predicted delivery date of the present pregnancy was May 19 1960 The patient s general condition had been fairly good throughout her preg rancy (Hgb 12-13 g albumin and glucose tests were negative weight increase under 10 kg the blood pressure 110-120/90 mmHg and Wasserman test negative) In the evening of May 9 1960 the patient felt exceptionally lively fœtal movements On the following morning the patient felt diffuse pains in her abdomen and the fundus of the uterus seemed subsequently to become firm and the right cornual region became tender The patient came to hospital without delay Fœtal heart sounds were not heard with certainty The patient had felt something like fœtal movement immediately before the attack of pain Examination established that the uterus was slightly contracted and the right cornual region appeared to be tender The cervix admitted a fingertip and the cervical canal was almost completely intact The situation most resembled premature placental detachment but there were no signs of shock It was known from earlier examinations that the fœtus was very large In the obvious absence of a chance of rapid delivery by the

Rhen K and Kinnunen, O., Acta obst. et gynec. scandinav 41 86, 196–

From the Private Hospital Mehilainen, Helsinki (Niilo Heinänen, M D)

ANTE-PARTUM RUPTURE OF THE UMBILICAL CORD

Case Report

BY

KURT RHEN AND OLAVI KINNUNEN

The reasons for rupture of the umbilical cord in connection with parturition have been summarised in detail by Matusovszky (1926), Joseph and Kohn (1926), Kopp (1937) and quite recently by Kessler (1960)

Thanks to its elastic structure and the tortuous course of its blood vessels the umbilical cord stands gradual stretching without breaking and hence can increase by as much as a third in length or, in terms of kilograms can take a load of 2 5–8 kg, according to different authorities However, rapid trauma, such as the falling of the child in precipitate labour, reduces the load capacity to about a third of the weight of the full term infant Such trauma usually causes *total rupture* of the cord This may occur also in connection with obstetric operative interventions such as internal version, forceps delivery or breech extraction Less common is *partial rupture* in which it is mostly the thin-walled veins that rupture Arterial ruptures are relatively much less common

Besides the above-mentioned traumatic causes of rupture of the umbilical cord, additional factors are changes in the anatomical structure (exceptionally short umbilical cord, coiling of the cord, velamentous insertion and varices) Histological structural changes such as paucity of elastic fibres or underdeveloped Wharton's cells also weaken the umbilical cord, and likewise various inflammatory processes Of the latter, special importance used to be attached to lues

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SUMMARY

The case is described of a multipara whose full term fœtus was lost on account of rupture of the umbilical cord before the onset of labour The cord was of normal length and had not coiled around the fœtus Autopsy showed that the development of asphyxia and fœtal death had been fairly slow, the infant having swallowed bloody amniotic fluid which had travelled as far as the small intestine The infant had made respiratory movements in the final phases of the asphyxia and blood had reached the lungs Histological examination showed that the venous walls at the site of the rupture were normal No clear explanation could be found in this case for the rupture of the umbilical cord before the onset of labour

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vaginal route Cæsarean section was decided upon with the indication *ablatio placentae ante tempus, asphyxia fœtus gravis*

Sectio Cæsarea isthmica transversa (Kinnunen) The liquor was found to be mixed with blood when the uterine wall was opened and the membranes ruptured No coagula were demonstrated A large, pale female baby (weight 4350 g, height 50 cm, head circumference 35 cm) was rapidly extracted but proved to be dead The placenta was located on the right in the anterior wall and was detached easily by light manual pressing No definite signs of ablatio were established in the placenta

The umbilical cord, which was 50 cm long, showed 3 cm from the umbilicus an uneven area measuring 1 cm × 1 cm in which a ruptured vein was established after the clot had been removed No other visible changes were observed grossly in the umbilical cord

Autopsy *(L Hjelt)* performed on the infant showed that she was well developed Thin fluid mixed with blood was observed in the bronchi on gross examination, the stomach contained approximately 10 ml of mucous, bloody fluid The content of the small intestine was fluid, mixed with blood, the large intestine contained greenish, solid meconium With the exception of anæmia, nothing abnormal was found in the internal organs

Microscopic examination showed that the lung tissue was completely devoid of air, the alveoli were full of amniotic fluid and hæmolysed blood which was present also in the bronchi The intestinal contents were mixed with blood and the red cells were partly disintegrated Serial preparations made from the umbilical cord displayed dilated veins and arteries, the histological structure of their walls, however, was normal The venous wall had ruptured at one point but nothing was found in the wall that could account for the rupture

It was thus obvious on the basis of the operative and autopsy results that the primary cause of the death of the infant was rupture of the umbilical cord This probably resulted in fairly slow asphyxia and death as the infant had had time to swallow so much blood containing amniotic fluid and the fluid had travelled as far as the small intestine It was obviously at the very end of the gradually developing asphyxia that the fœtus made respiratory movements and amniotic fluid mixed with blood penetrated the lungs

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Table II

Year	M		σ		V		No.	Sex of Infant Civil Status of Mother
1911/20	51.23	± 0.05	1.94	± 0.03	3.78	± 0.07	1 680	Girl Married
1921/30	50.83	0.03	1.90	0.02	3.74	0.04	3 699	
1931/40	50.63	0.03	1.80	0.02	3.57	0.04	3 929	
1941/50	50.55	0.03	1.87	0.02	3.72	0.04	4 978	
1951/56	50.53	0.04	1.91	0.03	3.77	0.05	2 685	
1911/20	50.99	0.04	1.94	0.03	3.81	0.05	2 777	Girl Unmarried
1921/30	50.69	0.04	1.93	0.03	3.80	0.05	2 943	
1931/40	50.32	0.05	1.76	0.04	3.50	0.07	1 288	
1941/50	50.23	0.06	1.86	0.04	3.70	0.09	931	
1951/56	50.51	0.08	1.84	0.06	3.67	0.11	569	
1911/20	51.88	0.05	2.06	0.03	3.99	0.07	1 865	Boy Married
1921/30	51.70	0.03	2.09	0.02	4.04	0.05	3 940	
1931/40	51.38	0.03	1.99	0.02	3.87	0.04	4 290	
1941/50	51.32	0.03	2.04	0.02	4.05	0.04	5 427	
1951/56	51.36	0.04	2.02	0.03	3.90	0.05	2 863	
1911/20	51.79	0.04	2.09	0.03	4.03	0.05	2 975	Boy Unmarried
1921/30	51.37	0.04	2.07	0.03	4.04	0.05	3 184	
1931/40	50.95	0.05	1.98	0.04	3.89	0.07	1 431	
1941/50	50.81	0.06	1.98	0.04	3.90	0.08	1 082	
1951/56	50.86	0.08	1.97	0.06	3.87	0.11	599	

cates that the secular trend toward larger size for a given age is still continuing in western Europe, America and Japan.

In an investigation (1961) of the length of the newborn during the last hundred years at the General Maternity Hospital, Stockholm, I have found that the length at birth of first born infants increased by 2–3 cm during the period 1857–1920 (Table I).

Since 1920 no increase, but rather a decrease, has been observed, as is shown in Table II.

As may be deduced from Table II, the length at birth has decreased by 0.6–1 cm, the difference being statistically significant.

M (Median) $\frac{\Sigma X}{n}$ σ (Standard Deviation) $= \pm\sqrt{\frac{\Sigma(X-M)^2}{n}}$

V (Coefficient of Variation) $= \frac{100\,\sigma}{M}$

Abolins J A Acta obst et gynec scandinav 41 90 1962
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AVERAGE LENGTH OF THE NEWBORN DURING THE LAST DECADES

A Preliminary Report

BY

J A ABOLINS

The standard Tables now used in assessing a child's physical development (Karlberg *et al*, 1955, Heimendinger, 1958, Tanner and Whitehouse, 1959, Stuart and Stevenson, 1959, and others) differ considerably from those previously employed In many investigations from west European countries a more rapid growth has been observed in infants, children of pre-school age, and schoolchildren (Broman, Dahlberg and Lichtenstein, 1942, Stephan, 1959, Milner Gulland, 1959, Stracker, 1959, and others) Many workers in this field predict that the increase in growth will continue The following paragraph concerning the standard Tables of Tanner and Whitehouse is taken from the Lancet, 1959 Doubtless they will soon be out of date, for all the evidence indi

Table I

Sex	Civil Status of Mother	Year 1857/60	Year 1910 20
Girl	married	48 35 cm	51 23 cm
Girl	unmarried	48 47	50 99
Boy	married	49 11	51 88
Boy	unmarried	49 08	51 79

Table II

Year	M		σ		V		No.	Sex of Infant Civil Status of Mother
1911/20	51 23 ±	0 05	1 94 ±	0 03	3 78 ±	0 07	1,680	
1921/30	50 83	0 03	1 90	0 02	3 74	0 04	3 699	
1931/40	50 63	0 03	1 80	0 02	3 57	0 04	3 929	Girl Married
1941/50	50 55	0 03	1 87	0 02	3 72	0 04	4 978	
1951/56	50 53	0 04	1 91	0 03	3 77	0 05	2 685	
1911/20	50 99	0 04	1 94	0 03	3 81	0 05	2 777	
1921/30	50 69	0 04	1 93	0 03	3 80	0 05	2 943	
1931/40	50 32	0 05	1 76	0 04	3 50	0 07	1 288	Girl Unmarried
1941/50	50 23	0 06	1 86	0 04	3 70	0 09	931	
1951/56	50 51	0 08	1 84	0 06	3 67	0 11	569	
1911/20	51 88	0 05	2 06	0 03	3 99	0 07	1 865	
1921/30	51 70	0 03	2 09	0 02	4 04	0 05	3 940	
1931/40	51 38	0 03	1 99	0 02	3 87	0 04	4 290	Boy Married
1941/50	51 32	0 03	2 04	0 02	4 05	0 04	5 427	
1951/56	51 36	0 04	2 02	0 03	3 90	0 05	2 863	
1911/20	51 79	0 04	2 09	0 03	4 03	0 05	2 975	
1921/30	51 37	0 04	2 07	0 03	4 04	0 05	3 184	
1931/40	50 95	0 05	1 98	0 04	3 89	0 07	1 431	Boy Unmarried
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cates that the secular trend toward larger size for a given age is still continuing in western Europe America and Japan

In an investigation (1961) of the length of the newborn during the last hundred years at the General Maternity Hospital Stockholm I have found that the length at birth of first born infants increased by 2–3 cm during the period 1857–1920 (Table I)

Since 1920 no increase but rather a decrease has been observed as is shown in Table II

As may be deduced from Table II the length at birth has decreased by 0 6–1 cm the difference being statistically *significant*

M (Median) $= \frac{\Sigma x}{n}$ σ (Standard Deviation) $= \pm\sqrt{\frac{\Sigma(X-M)^2}{n}}$

V (Coefficient of Variation) $= \frac{100\,\sigma}{M}$

I will not enter into possible explanations of this fact at present I believe, however, that my observations will be of interest to obstetricians, as no similar observations have, to my knowledge, been reported in the medical literature

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CLEIDOCRANIAL DYSOSTOSIS

Report of a Case

BY

JOHAN IVERSEN

Cleidocranial dysostosis has derived its name from the characteristic deficient or delayed ossification of the clavicles and skull Patients with this deformity, however, often show malformations in other areas of the skeletal system, and at times other organ systems are involved too From an obstetrical point of view, changes affecting the pelvis are of particular interest

In the first monograph on cleidocranial dysostosis (Hultkrantz 1908) pelvic deformity was mentioned in 7 out of 63 cases Hultkrantz interpreted the changes as a sign of abnormal stress upon weak bones, unlike the clavicular and cranial malformations which were called primary In 1921 Crouzon and Bouttier (1921) described a case with an additional finding of a broad pubic symphysis due to deficient ossification in the pubic rami In these authors opinion this was a special form of dysostosis and they suggested the name "forme cleido cranio pelvienne" Leroy *et al* (1953) reported a case with practically the same symphyseal defect They too believed that they were dealing with a special form of the disease It is doubtful however whether this can be maintained as similar changes have been described by several other authors (Bessere 1950 Kaner *et al* 1952 Eisen 1953) In addition to this defect and the narrowed pelvis changes may be observed around the acetabulum in the form of flattening and in the neck of the femur in the form of congenital

I will not enter into possible explanations of this fact at present I believe, however, that my observations will be of interest to obstetricians, as no similar observations have, to my knowledge, been reported in the medical literature

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Fig 1

In 1958 she became pregnant for the first time Since at that time her disease was considered disabling induced abortion was performed in another clinic In 1960 she had again become pregnant Now her situation was more stable and she wished to complete the pregnancy In the last trimester her pelvis was X rayed The films showed deficient ossification around the symphysis as evident from Fig 2 Accurate pelvimetry could not be performed as the symphysis did not show up distinctly in the lateral view On vaginal examination the diagonal diameter was estimated at about 11 cm but the sacral promontory could not be palpated with certainty It was decided to perform Cæsarean section at the onset of labour which occurred at the expected time In the course of the operation the true conjugate diameter was found to be 10 2 cm and the pelvis was funnel-shaped the minimum measurements being in the mid pelvis and the narrowing affecting mainly the transverse diameter The patient was delivered of a live girl of 2 300 g and 47 cm. The puerperium was uneventful.

The baby exhibited typical signs of cle docranial dysostosis having large fontanelles and wide sutures as well as a small but palpable defect of both clavicles In addition she lacked ossification centres around the symphysis pubis

coxa vara In children with cleidocranial dysostosis there may be symphyseal changes which must be presumed to be destined to develop into a similar defect Thus, Eisen (1953) as well as Schafer (1956) have reported absence or delay in growth or fusion of epiphyses and ossification centres in the bones which make up the pelvis

Since fertility does not appear to be reduced in these patients, complications may arise in connection with pregnancy and delivery For the mother's sake, the pregnancy will often have to be terminated by Cæsarean section because of the decreased pelvic measurements As far as the infants are concerned, brain lesions are common, since owing to the cranial defect they have little protection during the passage through the birth canal especially in the event of instrumental delivery There have been cases, however, in which the fœtus has been full term and has passed unharmed through an even greatly narrowed pelvis because of the greater compressibility of the head (Bessere, 1953, Nettesheim, 1926)

Present Case

A woman with cleidocranial dysostosis was admitted to the Maternity Department Her characteristic appearance is seen in the two figures Fig 1 shows the typical changes of the head, which is distinctly brachycephalic – a caput quadratum with prominent tubera frontalia separated by a deep midgroove at the site of the sagittal suture Dental deformities, as frequently seen in this disease, and slight mandibular prognathism owing to a poorly developed upper part of the face were also present *Fig 2 gives an impression of the abnormal mobility of the shoulders due to the clavicular* defect On both sides the lateral parts of the clavicles were replaced by *a fibrous* cord The patient was of small stature, measuring 150 cm Her weight, before the onset of pregnancy was 40 5 kg

The disease had been diagnosed as early as the age of 2 ½ months when she was admitted to a pediatric department because of anorexia and weight loss (Friderichsen 1939) Since then she had done tolerably well and there had been no particular difficulties but she was said to have been a rather delicate child After leaving school she had earned her living as a seamstress She is the elder of a family of two her younger brother – like her parents – being healthy, without any malformations The same is true of her maternal grandparents The father of her child was also normal and there were no known cases of dysostosis in his family



Fig 3

are often found This is presumed to be explicable by a rather commonly occurring mutation which is then transmitted as a dominant gene (Lasker 1946) In this case the mutation must be assumed to have taken place in one of the patient s parents, since her family was apparently completely normal On the other



Fig 2

Discussion

As is apparent from the above description, the patient showed the typical changes of cleidocranial dysostosis In addition to these, she had a symphyseal defect and narrowing of the pelvis, especially in its transverse diameter – also a common finding in this disease The pregnancy was terminated, as in so many other cases of the same nature by Cæsarean section The infant showed changes which must be presumed to develop into the same defects as the mother exhibits

The ætiology of this disease is unknown It is due to a defect of ossification, affecting primarily bones which ossify from membrane, but may also involve those which ossify from cartilage This happened in our case and caused the symphyseal defect Cleidocranial dysostosis was originally described as a hereditary disease by Marie and Sainton (1898), but sporadic cases



Fg 3

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hand, the infant has typical defects, showing exactly the same changes as her mother Thereby the gene has been transmitted, and the disease will continue by dominant inheritance Half the patient's descendants must, therefore, be expected to be born with the changes described above

In this case the offspring was a female, but both sexes are *equally affected However, there seems to be more tendency* for dysostotic mothers to bear girls having the defect and for fathers affected with dysostosis to beget boys suffering from the disease (Herndon, 1951) As a rule, the disease will then persist for about 3 generations and thereafter disappear from the family This is presumed to be due to selective mating', *i e* on an average only about 50 per cent of the patients get married and thus transmit the gene to the next generation In this form of selection the comparatively large number of patients who die without *progeny in each generation counterbalances the incidence* of the mutation in question

SUMMARY

Cleidocranial dysostosis is often accompanied by pelvic malformation The present report describes a woman, aged 23 in whom the typical changes co-existed with a symphyseal defect and pelvic narrowing Her first delivery was terminated by *Cæsarean section, and the infant had the same malformations* The disease often arises by mutation and is transmitted by dominant heredity, half the descendants being assumed to become affected

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ECLAMPSIA - A DISEASE OF CHECKED MICROCIRCULATION

BY

ROBIN FÅHRÆUS

There is no doubt about the ætiology of eclampsia The *primum mobile* is pregnancy But the way in which this physiological process gives rise to the serious disease – the most tragic complication of pregnancy – is still in many respects an unsolved problem in spite of the fact that a strong foundation for our knowledge was laid towards the end of the last century Since then an enormous amount of work has been done towards clearing up the question But the pathogenesis of the fundamental vascular disturbance remains obscure (Sheehan, 1950)

In the middle of the eighteen eighties Pilliet described the changes in the liver which he regarded as specific for eclampsia He postulated that the first stage of the disease is characterized by enormous dilatation of numerous capillaries in the periphery of the liver lobules The ectasies filled with thrombi are spherical and grouped like the grapes in "une grappe de raisin He regretted that it was not possible to combine this new finding with any of the many theories concerning the nature of the disease He showed that these specific alterations are followed by secondary changes such as atrophy, degeneration, and necrosis of the liver cells with infiltration of leucocytes and fibrinous thrombi

The classical work by Schmorl appeared in the year 1893 and concentrated also on changes in the liver He pointed out



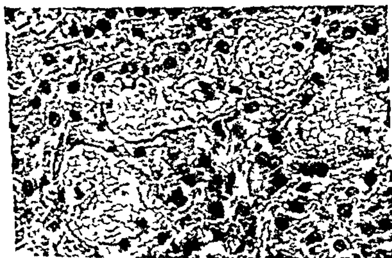


Fig 1 The ectasies of the liver in a case of eclampsia Enlargement 160 and 640 times respectively Para III aged 29 5 convulsions before 6 after admittance Blood-pressure 200/140 mm Hg during the last convulsion shortly before death. (By courtesy of L. Zettergren M D)

the general occurrence of thrombi, which he divided into two different types, namely the hyaline and the fibrinous The hyaline thrombi he describes in the following words Schon bei der Untersuchung von dem frischen Organ entnommenen Schnitten findet man sehr haufig, dass zahlreiche Kapillaren und kleine Venen so vollgestopft sind mit roten Blutkorperchen, dass diesel ben unter Verschwinden ihrer Konturen zu einer homogenen, roten, glasigen Masse zusammengezintert sind, welche das Lumen der betreffenden Gefasse prall ausfullt ' (See Fig 1) Schmorl added that it is perhaps erroneous to call these structures thrombi as they contain neither fibrin nor platelets These ectasies and their content have been the subject of many investigations, which have not been able, however, to explain their nature (Denecke, 1924)

A similar description of the liver in eclampsia was given by Welch (1909) Most of these cases show considerable hæmo lysis The masses described as fibrin in the hæmorrhages of the liver do not appear as clear cut fibrin fibrils, but have a hyaline appearance, which in places appears like fused red blood cell stromas One finds also in places within the vessels agglutinated red cells, which also fuse into hyaline appearing masses The author proposed the question Can we not explain the numerous hæmor rhages by assuming from our findings that there is circulating in the blood a poison which causes agglutination of the red cells, which then form emboli and by the solution of the endothelium of the blood vessels an easy means of escape of the blood?

The common opinion was once that the diseased kidney played the leading part in the pathogenesis of eclampsia, but after the work of Schmorl the changes in the kidney were placed in parity with those of the liver Fahr (1924) made a close study of the eclampsia kidney He found the glomeruli distended and as a rule bloodless, but sometimes filled with red corpuscles which had lost their outlines, thus forming homogenous masses He did not consider these thrombi to be as common as did Schmorl, but added the following words Immerhin habe auch ich diese Kapillarthromben ab und zu gefunden, manchmal ist es nicht leicht zu sagen, ob es sich um eine Thrombusbildung handelt, man sieht hier in Lumen der gequollenen Schlingen in der Form ver

As to the influence of pregnancy upon the relative number of erythrocytes, opinions differ All authors seem to agree, however, that there is an increased destruction of red cells during the last months of pregnancy, counterbalanced by an increased production (Denecke, 1924)

In eclampsia, on the contrary, as a rule one finds a rapid and sometimes enormous increase in the relative number of the erythrocytes Zangemeister (1903) stated that figures of 6–7 millions are not rare In one case he found 9 36 millions per cubic mm Skajaa (1929) found that an increase of 20–30 per cent in the relative number of the red cells is common during the height of the disease *This explains* the increased viscosity of the blood in eclampsia which according to Engelmann (1926), is on an average increased by 40 per cent.

The cause of this unique hæmoconcentration is that a great part of the plasma leaves the vascular system through the capillary walls, giving rise to œdema The mechanism, well known since its discovery by Vaquez (1897), is, that the blood pressure is increased suddenly especially shortly before and during the fits *According to* Wimhöfer *and* Pfau *(1956) thus sign appears in* 94 per cent of all cases A supporting factor is probable an increased permeability of the capillary walls which also reveals itself through the common occurrence of œdema during pregnancy Once the circulatory disturbance has started hypoxæmia aggravates the leakage

The œdema fluid consists of water and parts of the small sized protein fractions As a consequence the fibrinogen and probably also the serumglobulin, together with the *erythrocytes* become concentrated in the remainder of the plasma The serious outcome is that an already high fibrinogen content is further increased

Two hundred years ago the influence of the fibrin upon the sedimentation of the red cells was a great hæmatological problem

During his study of the origin of the buffy coat Hewson (1739–1774) found that the sedimentation rate of the red cells was *very much greater in plasma than in serum* which he tried to explain by the paradoxical supposition that "the coagulable lymph" makes the serum thinner less viscous

änderte und verklumpte rote Blutkorperchen liegen, bei denen es sich schon um den Beginn einer Agglutinations- resp Konglutinationsthrombose handelt

The oldest known alteration of the blood during pregnancy is the buffy coat or inflammatory crust referred to by Empedokles, when he stated that the blood of the pregnant woman is altered to a white beast This phenomenon occurs when the sedimentation rate of the red corpuscles is so great that they have time to subside from the surface layer of the blood before it clots In the pathology of antiquity the buffy coat was a symptom that the most injurious of the four fluids, the cold and humid phlegm, had risen and overthrown the three others That is the first known observation of the fact that the fibrin is increased during pregnancy, i e that there exists a *physiological hyperinosis*

Some of the first estimations of the fibrin content of the plasma during pregnancy were made by Nasse (1876) He found that the fibrin content in the non-pregnant woman is 0 26 per cent and that during the last months of pregnancy this value rose to 0 46 per cent During eclampsia the relative content of fibrin was still further increased Kollmann (1897) noted in three cases a mean value of 0 77 per cent and drew the conclusion that eclampsia was the consequence of a globulin poisoning This idea was taken up by Dienst (1902), who found very high plasma fibrin values, in one case as much as 2 8 per cent He regarded the increase of this protein as being responsible for the fibrin thrombi found in different organs at *post mortem* examination Dieckmann (1952) gave the following survey of the fibrin values

Non pregnant healthy woman	0 26 %
Pregnant healthy woman	0 46 %
Woman with pre-eclampsia	0 51 %
Woman with eclampsia	0 66 %

There is reason to believe that the last-named mean value is low by inclusion of late cases of eclampsia, where the fibrin is used up by the process of extended fibrinous thrombosis In this later phase of the disease afibrinogenæmia is not uncommon

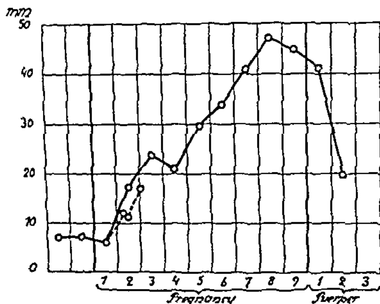


Fig 2 The sedimentation rate of the erythrocytes before during and after pregnancy

spondence *in vivo*, that is to say that the red cells are to a larger extent aggregated in the flowing and stagnant blood of the preg nant woman as compared with the non pregnant and further that this characteristic is still more pronounced in patients with ec lampsia

As shown above there is reason to believe that a suddenly in creased concentration of fibrinogen occurs during the culmination of the disease due to the hæmoconcentration A similar alteration in the blood can easily be imitated by evaporation of the plasma by means of an air current at room temperature Fig 3 demon strates at 17 times enlargement a 40 per cent erythrocyte sus pension in native and in double concentrated heparin plasma re spectively

The two upper photos represent the erythrocytes from a healthy man suspended in his native and his double concentrated plasma respectively The two lower photos in the same Fig show the comparable result with the blood from a woman in the tenth month of pregnancy The red cells in the native plasma exhibit

When Nasse (1836) considered the same problem he found that the most characteristic property of the buffy blood was the great tendency of the erythrocytes to aggregate and this gave rise to the raised sedimentation rate He was well aware of the difference in the sedimentation rate of the red cells in plasma and in serum respectively But nevertheless he regarded the importance of the fibrin as limited to the origin of the buffy coat He gave two reasons for this He said that the red corpuscles surely sink faster in plasma than in serum, but the *difference* in sedimentation rate between normal and buffy blood persists after defibrination He stated further that there is a group of disease such as typhus, malaria, and sepsis in which great aggregation and rapid sedimentation of the red cells occurs, although the fibrin values are normal

The exceptions from the rule that the sedimentation rate of the erythrocytes depends upon the relative amount of fibrinogen in the plasma are explained by the increased amount of serum globulin This fraction of the plasma proteins was not known in Nasse's time and its aggregation capacity was not discovered until 1921 (Fahræus)

The curve in Fig 2 shows the mean values of the erythrocyte sedimentation rate in the months before, during, and after normal pregnancy and gives approximately the relative degree of erythrocyte aggregation throughout the gestation period In patients with eclampsia a definite elevation of the sedimentation rate is seen (Oettingen, 1921, Malmnas, 1958, Dhall and Taneja, 1960), in spite of the erythrocytosis which gives sedimentation values which are too low in relation to the fibrinogen percentage of the plasma Forty years ago I published a case of eclampsia with 7 1 million erythrocytes per cubic mm and a sedimentation rate of 63 mm in one hour, figures which together represent an enormous tendency to aggregation of the red cells Of special interest is the observation by Malmnas that in cases of toxemias of pregnancy the abnormally high sedimentation rate sets in before albuminuria, œdema and hypertension make themselves known

In these days it is not necessary to emphasize that the aggregation tendency of the erythrocytes *in vitro* has its complete corre-

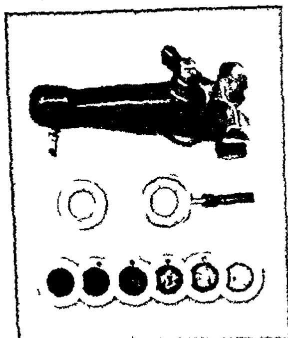


Fig 4 Apparatus for determining the filterability of the blood The 6 papers show the distribution of the erythrocytes in an experiment with blood from a case of myeloma with great aggregation tendency of the erythrocytes

head the stream and collect most richly in the lower papers of the pile In the concentrated plasma on the other hand they form aggregates which are to a great extent caught in the upper papers of the pile

Fig 6 gives a conception of the different degree of aggregation of horse erythrocytes in solutions of serum albumin serum globulin and fibrinogen produced by precipitation of horse plasma (Fåhraeus 1921) Some experiments have now been made with human erythrocytes suspended in fibrinogen solutions obtained by precipitation of human plasma The figures below show the sedimentation rate of the erythrocytes in fibrinogen solutions of different strengths (The fibrinogen was kindly supplied by AB Kabi Stockholm)

Sedimentation in mm in 1 hour 0.5 % – 2 mm 0.75 % – 20 mm 1 % – 40 mm 1.5 % – 80 mm 2 % – 110 mm



Fig 3 Enlargement 17 times Above A 40 per cent erythrocyte suspension healthy man Below A 40 per cent erythrocyte suspension, pregnant woman. To the left with native, to the right with concentrated plasma.

in this case about the same degree of aggregation as the red cells of the healthy man in the double concentrated plasma, in accordance with the fact that the fibrinogen content must be about the same in either case If we accept the data of Dieckmann (1952) given above, the double concentration of the plasma of the pregnant woman must correspond to a fibrinogen percentage of more than 1 per cent In this case the aggregates are not only greater, they are also, as appears from microscopic study much more solid than the smaller aggregates in the native plasma

The combination of size and solidity of the aggregates can be estimated approximately by the behaviour of the erythrocytes in a porous material such as filter paper A method of determining the filterability of the erythrocytes is described elsewhere (Fahraeus, 1961) The apparatus used and the result in a case of myeloma with a very great aggregation tendency of the erythrocytes are shown in Fig 4

Curve 1 in Fig 5 shows the relative concentration of haemoglobin in the 6 papers, when the red cells from a healthy man have been suspended in his native plasma and Curve 2 in his double concentrated plasma In the former case the erythrocytes

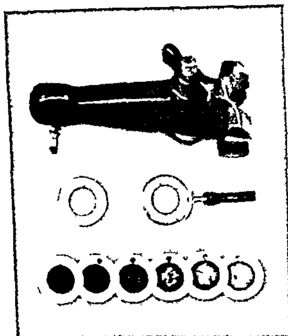


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Sedimentation in mm in 1 hour 0 5 % – 2 mm 0 75 % – 20 mm, 1 % – 40 mm 1 5 % – 80 mm 2 % – 110 mm

Fig 5 The distribution of the erythrocytes in a pile of 6 filter papers, Curve 1 suspended in native plasma and Curve 2 in concentrated plasma.



Fig 6 The aggregation of horse erythrocytes in solutions of serum albumin, serum globulin and fibrinogen. Enlargement 4 times

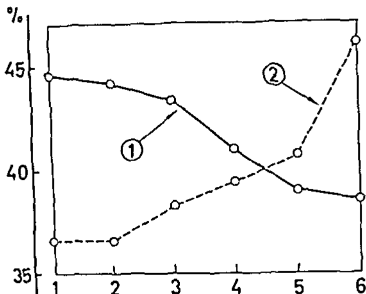


Fig 7 The distribution of the erythrocytes of a 40 per cent suspension in a pile of 6 filter papers Curve 1 represents the result with a 2 per cent fibrinogen solution, Curve 2 with a 0 5 per cent solution

Fig 7 shows a comparison between the distribution of the erythrocytes in a pile of filter papers when they are suspended in a 2 per cent solution (Curve 1) and in a 0 5 per cent solution of fibrinogen (Curve 2) The suspensions contained 40 per cent erythrocytes In the weaker fibrinogen solution the red cells penetrate to the deeper parts of the paper pile, while the movement of the large aggregates in the stronger solution is checked and they therefore collect in the upper papers of the pile

Morphological pathology and hæmatology together with the results of these simple experiments, give rise to the question whether the *hyaline thrombi in the ectasies of the liver capillaries* and in other vessels are not consequences of the pathological hyperinosis

If in conformity with **Schmorl Welch** and **Fahr** we admit

that these formations consist only of red cells, they are correctly characterized as aggregates of erythrocytes. Welch's question whether there exists a poison, circulating in the blood, with the capacity of aggregating red cells is thus answered, there does exist such a substance in the circulating blood, which in concentrations above the normal may be called a strong agglutinin for the erythrocytes, namely *fibrinogen*.

In his classical study on thrombosis Beneke (1913) raised the same question. He was of the opinion that an agglutinin must exist to explain the pathological anatomical alterations, including those seen in eclampsia, which are similar to the changes resulting from injection of hæmagglutinating sera. He foretells what seems to me the result of this investigation with the following words: 'Vielleicht erledigt einmal die Entdeckung eines einzigen 'Agglutinins' eine Fülle von Fragen mit einem Schlage.' I believe that the agglutinin sought for is nothing more than an increased percentage of fibrinogen, often associated with an increased concentration of serum-globulin.

Thus the aggregation of the red cells explains the vascular disturbance. The massive aggregates get the character of emboli, appearing most distinctly in the ectasies of the liver. The erythrocytes are here pressed together without any plasma being left – a morphological analogy to the hæmoconcentration. The outlines of the red cells are still discernible and give evidence that the normal form has been lost.

The embolic effect of the erythrocyte aggregates probably explains also the principal clinical symptoms of eclampsia, the convulsions and the coma. Through embolism brought about by a suspension of *Lycopodium* spores (0.030 mm in diam.) injected in the left ventricle of the heart of rabbits convulsions and coma are produced, followed by death, if the dose is sufficiently great (Fahræus, 1960).

In this connection it is of interest to establish that incompatible blood transfusion produces a symptom-complex of hypertension, œdema, convulsions and anuria, in essential respects a copy of eclampsia. See a case published by (Dieckmann, 1952, p. 347). There is hardly any doubt that this is an effect of erythrocyte aggregates.

Pflugbeil (1903) once declared Die Eklampsie kommt durch eine pathologische Steigerung normaler, der Schwanger schaft eigentümlicher Veränderungen zustande This applies at least to the increased fibrinogen of the plasma and to the increased aggregation of the erythrocytes

But there are certainly several other processes involved in the pathogenesis of eclampsia Besides the hyperinosis and the in creased aggregation of the erythrocytes, there seem to be hypox æmia increased permeability of the capillary walls, hypertension with œdema, erythrocytosis and hæmolysis The typical rapid progression of the disease from a state of complete health to potential or actual death favours the belief that these processes co-operate in a vicious circle

Between two of them, namely hæmolysis and hyperinosis, there seems to be a close causal connection Reymann (1924) found that anæmia in horses used for the production of serum, was followed by an increase of the fibrinogen percentage of the plasma He drew the conclusion that the red corpuscles destroyed leave material for the production of fibrinogen We have made experi ments on rabbits which support this conception (Fagerberg, F, Fagerberg S E and Fåhræus R, 1941) Different proce dures which bring about hæmolysis (intravenous injection of water or lysolecithin or of centrifuged red cells from another rabbit) give rise to an increased fibrinogen content of the plasma

SUMMARY

The pathological anatomy of eclampsia is in its first phase characterized by so-called hyaline thrombi which, judging from the literature are identical with aggregates of erythrocytes As a consequence several of the leading pathologists have sought for a substance in the blood with the capacity of aggregating the red cells Actually such a substance is to be found in two of the protein fractions of the plasma namely the fibrinogen and to a lesser extent the serum globulin The fibrinogen especially is in normal concentration already an "agglutinin" and increases in amount during normal pregnancy and further increases in eclampsia The effect of this alteration of the plasma is the for

mation of large solid aggregates of erythrocytes, which act as emboli and explain the fundamental vascular disturbance

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THE EFFECT OF INTRA-AMNIOTIC INJECTION OF HYPERTONIC SODIUM CHLORIDE IN HUMAN MIDPREGNANCY

BY

LARS PH BENGTSSON AND NILS STORMBY

There are several methods for starting myometrial activity in the human uterus in midpregnancy Some of them have been used for induction of therapeutic abortion Of interest in this connection are artificial rupture of the membranes (Oram, 1948, Kühnel, 1952 Asplund and Bryhn 1957, Bengtsson and Kullander 1959) intrauterine injection of hypertonic solutions (Aburel 1948 Cioc 1948 Kovacs 1948 Stamm and de Watteville 1954 Szecsi 1955 Brosset 1958 Svane, 1960 Bengtsson and Csapo 1962) and intra amniotic injection of formalin (Nölle 1948 Bengtsson, 1959) In spite of numerous publications on such methods, analyses of their effective mechanism are rare It is obvious, however that a careful study of the effective mechanism should throw light on the control of myometrial activity in pregnancy and parturition, a problem of great theoretical and clinical significance

In a recent investigation, Bengtsson and Csapo (1962) studied the effect of intra amniotic injection of 20 per cent sodium chloride on myometrial activity in cases of therapeutic abortion in midpregnancy The present investigation of the effect of intra amniotic 20 per cent saline injection on foetus foetal membranes

placenta and myometrium was performed in an attempt to elucidate how the increased myometrial activity is produced.

Technique of injection

The amniotic sac was punctured through the abdominal wall, and 100–250 ml of amniotic fluid was withdrawn This was followed by the injection of about the same amount of sterile 20 % sodium chloride solution Spontaneous myometrial activity started within a day, and abortion was completed on an average within 34 hours (Bengtsson and Csapo, 1962) In two cases, kindly placed at our disposal by Dr A Brosset, Molndal, 50 % glucose was injected instead of saline

Series

Nineteen out of 24 cases of therapeutic abortion induced by means of intra-amniotic injection of hypertonic saline reported elsewhere (Bengtsson and Csapo, 1962), were analyzed histologically Each placenta was examined, at least six blocks being taken from different parts As a rule the whole depth of the placenta from the amniotic to the uterine surface was present in one continuous section Sections were also taken from the umbilical cord and its placental insertion The sections (5 μ) were stained with hæmatoxylin-eosin

Results

Fœtal death ensued some few hours after saline injection This was accidentally discovered in 4 cases in the series of Bengtsson and Csapo (1962) In these cases the intra-amniotic catheter was constantly moved by the fœtus, whose movements were recorded by the recording apparatus These movements stopped 2–4 hours after saline injection In one case a hysterotomy was performed 4 hours after saline injection a freshly dead fœtus was found

On the body surface of all fœtuses numerous small red spots were observed Histologically these spots consisted of greatly



Fig 1 Placenta 18 hours after NaCl injection × 145 a) The membranes b) Areas of severe placental damage c) More normal placental tissue

dilated cutaneous and sub-cutaneous vessels filled with blood Sometimes there was also extravasation of red blood corpuscles into the adjacent tissues No changes were seen in the internal organs Thus the picture was not that seen in anoxia The cause of these hæmorrhages is presumably a direct effect of the hypertonic fluid on the skin of the fœtus

In all cases *the placenta* was macroscopically œdematous and flabby Very often fresh hæmorrhages were visible under the amniotic surface too numerous to have been produced by the single insertion of the needle *Microscopic examination* of the placenta showed severe damage localized mainly to a layer some millimetres thick under the membranes (fig 1) In the early stage(four hours after saline injection) the changes were



Fig 2 Pronounced vacuolization of the trophoblast (4 hrs after NaCl injection) × 840

characterized by a gross fibrinous hæmorrhagic intervillous exudate and œdema of the villi with incipient destruction of the trophoblast An interesting finding was a pronounced vacuolisation of the syncytiotrophoblast and the cytotrophoblast This vacuolization was obvious in cases with a short interval between saline injection and abortion after a longer interval the phenomenon was seen only occasionally The most distinct vacuolization was observed in the placenta from the patient upon whom hysterotomy was performed four hours after saline injection (fig 2) Most probably the changes were due to the osmotic effect on the cells

In the interval between saline injection and abortion the inflammatory exudate between the villi became progressively more cellular with numerous polymorphonuclear leucocytes (fig 3) The villi directly beneath the membranes were necrotic and invaded by leucocytes The inflammatory process also involved deeper layers of the placenta with œdema of the villi destruction of the trophoblast and leucocytic exudate, but histological changes



F g 3 Destruct on of the v lli and appearance of many polymorphonuclear leucocytes × 210



Fig 4 Interst tial œdema in the membranes × 210

were not usually demonstrated in the uterine half of the placenta Histological examination of the umbilical cord showed nothing remarkable in most cases, in occasional cases fresh thrombosis of the umbilical vessels was noted

The placentas from the two abortions induced by intra amniotic 50 per cent glucose showed substantially the same changes as described above This suggests a common ætiological factor the hypertonicity of the fluid injected

The membranes were macroscopically œdematous and flabby, almost jelly-like It is possible that these changes accounted for the rapid rupture of the membranes which sometimes happened shortly after the start of uterine contractions Histologically the membranes often showed considerable interstitial œdema (fig 4) This is in accordance with the findings of Stamm and de Watteville (1954) Sometimes, also small necrotic foci with polymorphonuclear leucocytes were observed

The myometrium was examined in one case only, which was operated upon 4 hours after intra-amniotic injection of saline (hysterotomy + salpingectomy) The excised wedge of the myometrium showed microscopically normal muscle tissue without trace of inflammatory changes Small foci of inflammatory cells, mostly lymphocytes, were observed in the decidua (fig 5)

Discussion

The observation of œdematous membranes after saline injection confirms the findings of Stamm and de Watteville (1954) No study of the placenta, fœtus or myometrium after hypertonic *intra* amniotic injection has been reported previously

The placental function is of crucial importance when considering the cause of myometrial activity after intra-amniotic injection of saline It should be possible to draw certain conclusions concerning this function from the macro- and microsopic picture of the placenta Macroscopically the entire placenta was œdematous, indicating damage to the whole organ Microscopically a necrotizing placentitis was observed in the layer beneath the fœtal surface, slowly decreasing towards the maternal surface Thus, from the



Fig 5 The excised wedge of myometrium and decidua 4 hrs after intra amniotic injection of saline × 110

macro and microscopic examination it is evident that big areas were severely damaged

Thus severe damage to the placenta would probably result in a rapid decrease in placental hormonal production which would in turn be followed by a decrease in the urinary excretion of placental hormones or metabolites Luukkainen (cit by Csapo 1961) found a fall in progesterone blood levels after intra amniotic injection of hypertonic saline In the present investigation pregnanediol excretion was determined in 6 cases by means of the method published by Jensen (1958) The day after saline injection the urinary pregnanediol excretion was on an average 46 per cent of the pre-experimental value Cassmer (1959) found in normal midpregnant women (therapeutic abortions) that when the fœtus and placenta were removed simultaneously the pregnanediol excretion fell to 43 per cent in 24 hours When only the fœtus died (ligation and severing of the umbilical cord) and the placenta was left intact (isolated placenta) the pregnanediol excretion was 89 per cent of the

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pre-experimental value one day after fetal death and 87 per cent three days later A rapid decrease in urinary excretion of oestrogens after intra-amniotic injection of hypertonic saline has been found by Fuchs (1961) Thus, the anatomical placental changes as well as the urinary excretion of oestrogen and pregnanediol indicate a rapid decrease of placental hormonal production Borth *et al* (1952), however, found no decrease in urinary pregnanediol excretion after intra-amniotic injection of 10 *per cent* saline The reason for this difference in pregnanediol excretion after intra-amniotic injection of 10 per cent and 20 per cent saline respectively is not known

No histological changes were observed in the myometrium 4 hours after saline injection This does not exclude the possibility of a direct effect on the myometrium, increasing activity but producing no microscopical changes As pointed out by Stamm and de Watteville (1954), however, such a direct effect should stimulate myometrial activity very soon after saline injection and not several hours later, when the amniotic tonicity approaches normal values These authors found a rapid decrease in the hypertonicity of the amniotic fluid produced by injection of hypertonic saline *This was confirmed in the present investigation* When the myometrial activity increased, the hypertonicity had declined considerably, and 16 hours after saline injection, when labour like activity was recorded, only slightly elevated values were found

It is well known that sodium chloride, irrespective of the route of administration, causes a release of oxytocin This effect also should be produced long before the amniotic fluid tonicity approaches normal values Since the myometrial activity does not start until several hours after the administration of sodium chloride, the onset of myometrial activity after intra amniotic injection of hypertonic saline is not due to a direct effect on the myometrium or to a release of oxytocin

From the observed changes in the placenta and the study of myometrial activity before and after saline injection, performed by Bengtsson and Csapo, it was possible to draw certain conclusions as to the endocrine control of the myometrium (Bengtsson and Csapo, 1962)

SUMMARY

In order to elucidate the factors which lead to abortion after tra amniotic injection of 20 per cent sodium chloride in midpreg ancy, a macro- and microscopical study of the fœtus, the placenta, he membranes and the myometrium was performed in such abor ions *The fœtus*, which died possibly a few hours after saline in- ection showed numerous red spots on the body surface, due to reatly dilated cutaneous and subcutaneous vessels No changes of he internal organs were observed *The placenta* was macroscopi ally œdematous Microscopically the trophoblast showed cellular hanges indicating osmotic damage Beneath the membranes a necrotizing placentitis was observed, decreasing towards the uterine part The changes are described in details The membranes were macro and microscopically œdematous In the *myometrium* no changes could be observed The mechanism of saline induced abortion is discussed

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It is well known that sodium chloride, irrespective of the route of administration, causes a release of oxytocin This effect also should be produced long before the amniotic fluid tonicity approaches normal values Since the myometrial activity does not start until several hours after the administration of sodium chloride, the onset of myometrial activity after intra amniotic injection of hypertonic saline is not due to a direct effect on the myometrium or to a release of oxytocin

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SUMMARY

In order to elucidate the factors which lead to abortion after intra amniotic injection of 20 per cent sodium chloride in midpregnancy, a macro- and microscopical study of the fœtus, the placenta, the membranes and the myometrium was performed in such abortions *The fœtus*, which died possibly a few hours after saline injection, showed numerous red spots on the body surface, due to greatly dilated cutaneous and subcutaneous vessels No changes of the internal organs were observed *The placenta* was macroscopically œdematous Microscopically the trophoblast showed cellular changes indicating osmotic damage Beneath the membranes a necrotizing placentitis was observed, decreasing towards the uterine part The changes are described in details The membranes were macro and microscopically œdematous In the *myometrium* no changes could be observed The mechanism of saline induced abortion is discussed

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EXPERIMENTS ON THE SUPPRESSIVE EFFECT OF A SYNTHETIC GESTAGEN ON THE ACTIVITY OF THE PREGNANT HUMAN UTERUS

BY

LARS PH BENGTSSON

Our present knowledge of the hormonal control of the myometrium of the pregnant uterus is based upon a series of important findings The discovery that destruction or removal of corpora lutea in pregnant rabbits terminates gestation (Fraenkel, 1910), the extraction of the active substance (progesterone) from corpora lutea (Corner & Allen, 1929), the discovery of the chemical structure of progesterone (Allen & Wintersteiner, 1934, Butenandt *et al* 1934, Hartman & Wettstein, 1934, Slotta & Ruschig, 1934) and the observation that progesterone is metabolized to pregnanediol, part of which is excreted in the urine (Venning & Browne, 1940), were all steps in the development of our current knowledge of the process

After these basic discoveries very little of importance was added to our knowledge in the field until Csapo attacked the problem from new points of view, studying the physiology, electro physiology, histology and biochemistry of the myometrium He and his co-workers (see Csapo 1955, 1956, 1960 and 1961) have to a great extent elucidated the hormonal control of the rabbit myometrium and have recently studied the human myometrium (Bengtsson, 1959 a and b, Hendricks *et al*, 1961, Bengtsson & Csapo, 1962, Bengtsson, 1962) In recent years extensive studies have been published on the oxytocin effect in animal and human pregnancies, especially by Caldeyro Barcia and his group (for refe

rences see Caldeyro Barcia, 1961), studies on blood levels of progesterone and pregnanediol (Forbes, 1951, Zander, 1955, Despahande & Sommerville, 1958, Aitken et al, 1958, Short, 1958, 1960, Short & Eton, 1959), on pregnanediol excretion (from numerous laboratories all over the world) and on the body distribution and metabolism of progesterone by means of labelled hormones (Davis & Plotz, 1956, 1957, 1958 Plotz, 1961, Pearlman, 1957, Sandberg & Slaunwhite, 1958, Zander, 1959, 1961) Finally, the production of synthetic gestagens from a great number of laboratories and pharmaceutical firms has opened new scientific and therapeutic possiblities

The present view of the role of the two most important steroid groups, œstrogens and gestagens, in controlling the myometrium of the pregnant uterus, is that œstrogen is necessary throughout pregnancy in all mammals to stimulate myometrial growth while progesterone is necessary throughout pregnancy in rabbits to keep the œstrogen stimulated myometrium inactive and non reactive to stimuli A still unsolved problem, however, is whether progesterone has the same role in human pregnancy

Many well known facts tend to deny the assumption of this role of progesterone in human pregnancy, the most important of which are (a) lack of certain proof of any effect of progesterone therapy in threatened or habitual abortion (b) intramuscular administration of progesterone is ineffective in threatened premature labour (Fuchs & Stakeman, 1960), (c) progesterone therapy does not produce any effect on myometrial activity or oxytocin sensitivity at term (Pose & Fielitz, 1961), and (d) there is no decrease in blood progesterone or pregnanediol excretion before the onset of labour (see Borth & De Watteville, 1952, Short & Eton, 1959)

As regards blood progesterone and pregnanediol excretion it should be realized that there are many unknown intermediary stages between progesterone production, blood progesterone and urinary pregnanediol Because of this no conclusions can be drawn from steroid blood concentrations or excretions concerning the hormonal situation in the myometrium A clear discrepancy between blood progesterone and the hormonal status of the myometrium has been shown in pregnant sheep (Bengtsson &

Schofield, 1960) Thus, for further knowledge of the hormonal control of the pregnant uterus, methods other than the determination of hormones and their metabolites in blood and urine must be used

Examples of such new approaches to this problem are the recent extensive studies of progesterone metabolism (see above), which have given valuable information, and Csapo's theory on the local hormone effect of the placenta (Csapo, 1959, 1961, Macedo Costa & Csapo, 1959) According to this theory progesterone, produced by the placenta, reaches the myometrium at the placental site directly, *i e* without passing the general circulation If that is so, the concentration of progesterone in the myometrium close to the placenta should be extremely high and should produce a very pronounced blocking of the activity of this area The effect should gradually decrease farther from the placenta Labour should start when the local dominating effect of the placenta decreases to a certain value in relation to the undominated area This theory has also got experimental support intra-amniotic injections of progesterone in pregnant rabbits are effective in very small doses, which have no effect if given systemically (Macedo Costa & Csapo, 1959), such injections in pregnant women are effective in suppressing myometrial activity also in late pregnancy (Hendricks *et al*, 1961)

Another hypothesis, which might explain the fact that circulating progesterone is capable of depressing uterine activity in midpregnancy (Bengtsson, 1959 a, Bengtsson & Csapo, 1962) but not at term (Pose & Fielitz, 1961) was presented some years ago (Bengtsson, 1959 b) near term there may be a change in progesterone metabolism, with the result that circulating progesterone never reaches the myometrium as an effective substance If that is so, the progesterone block (Csapo, 1956) is withdrawn as effectively as if the progesterone production had ceased (Bengtsson, 1959 b) This theory has not yet been proved, but some evidence which supports it has been presented (Bengtsson, 1959 b)

Both theories just mentioned try to explain why circulating progesterone is ineffective at term Furthermore, they both indicate that *if progesterone or any effective gestagen could be applied*

so as to produce a high concentration in the myometrium without being metabolized beforehand, it ought to be effective irrespective of the length of gestation

From these premises and inspired by the above mentioned experiments performed by Csapo (1959) and Hendricks *et al* (1961) on the suppressive effect of intra amniotic application of progesterone, the author started the experiments on intra myometrial injections of gestagens presented in this paper

Methods

Any fluid injected directly into the myometrium may act as an irritant, stimulating myometrial activity Any effect obtained may be influenced not only by the nature of the fluid but also by its volume It was therefore necessary to inject a highly concentrated and potent hormone Progesterone cannot be obtained in higher concentrations than 50 mg/ml oil On the other hand synthetic gestagens of much higher potency than progesterone are available in suspensions up to 100 mg/ml physiological saline For that reason 6α methyl 17α acetoxyprogesterone (*Provera*, *Upjohn*) was chosen This is claimed to be at least 4 times as potent as pure progesterone

In order to suppress myometrial activity it should be sufficient to produce a few strongly progesterone blocked areas in the anterior uterine wall These areas should stop the propagation of impulses through a considerable part of the anterior wall so that only limited contractions could develop in between the blocked areas Uterine contractions ought to decrease both in frequency and in strength

We do not know the physiological concentration of progesterone in the myometrium In these first series of experiments, therefore rather big doses were used in order to make the areas reached by diffusion of the hormone from the point of injection as large as possible

The total dose of Provera injected into the myometrium varied from 150–400 mg The Provera suspension injected contained 50–100 mg/ml Thus the maximum amount of fluid injected at each of the three points (see below) was 1 3 ml

Technique of injection The hormone was injected at three or four points of the anterior uterine wall in the region of each uterine cornu and at one or two points in the middle of the anterior wall By these means the pacemakers and the middle of the anterior wall should be damped The needle was inserted through the abdominal wall into the amniotic sack until amniotic fluid – or placental blood – could be aspirated The needle was then withdrawn until no fluid (or blood) was obtained While further withdrawing the needle 1–1 5 cm so that its tip was well into the uterine muscle, the hormone was injected By these means there was a reasonable chance that the hormone was injected into the myometrium In some cases most of the amniotic fluid had been lost and no blood could be aspirated (due to the location of the placenta), so the injection had to be done empirically

Recording of uterine activity In legal abortions the myometrial activity was recorded through an intra-amniotic catheter (Alvarez & Caldeyro-Barcia, 1954), in all other cases by means of an external tokometer (Malmstrom, 1957), connected to a recording unit, consisting of an Elema-Schonander pressure receptor (EMT 490 A), an Elema-Schonander electro manometer and a Varian ink recorder (Model G - 10) The latter gives a reliable picture of the frequency of the contractions but a somewhat less accurate picture of their absolute strength This strength has therefore been estimated partly by means of the recordings and partly by the patient s appreciation of the contractions A decrease of the recorded tension and frequency of contractions combined with subjective weakening or cessation of pain was judged as a real decrease in uterine activity In the presented records, artefacts, due to movement or coughing of the patient are excluded

Material Only cases with *effective* uterine activity were treated Thus, there were not only subjective and objective (recorded) uterine contractions but also one or several obvious signs of progress of labour effacement of the cervix, ruptured membranes and bleeding The different obstetrical situations are seen in Table I

Table I Summary of Cases Treated with Intra Myometrial Injection of Proluton The Cases are Arranged According to Position of the Fœtal Head

	Cases	No	Week of Gest	Symptoms	Condition of Cervix and Os	Effect
I	Therapeutic abortion	2	20	P	closed	++
	Premat labour	5	33	P B	closed	++
	Premat labour	6	35	P	1 finger	+
	Premat labour	7	28?	M P, B	½ effaced 1 finger	++
	Therapeutic abortion	1	19	P	½ effaced 1 finger	++
	Spont abortion	3	22	M P B	½ effaced 1 finger	++
	Premat labour	8	33	M P	effaced 1 finger	++
	Premat labour	9	35?	M P	effaced 1 finger	++
	Premat labour	10	33	M P B	effaced 1 finger	++
	Spont abortion	4	18	P B	effaced 1 finger	++
	Premat labour	11	34	M P B	effaced 2 fingers	o
II	Premat labour	12	32	M P	effaced 1 finger	+
	Premat labour	13	35	P	effaced 2 fingers	o
	Premat labour	14	29	P	effaced 2 fingers	o

I fœtal head in pelvic inlet
II fœtal head in pelvic cavity
M = ruptured membranes
P = pains
B = bleeding
The numbers correspond to the case numbers in text

++ = suppression of uterine activity
+ = incoordination of contractions but no suppression

It sometimes happens that uterine activity during pregnancy stops spontaneously Any attempt to stop such activity must therefore be repeated in a series of cases and reported in detail Fourteen cases are reported below, two legal abortions induced by intra amniotic injection of 20 % sodium chloride and 12 unselected cases of spontaneous abortion or premature labour

Results

A *Therapeutic abortions*

These two cases are the only ones in which the hormonal situation could be forecast recent investigations have indicated a decrease in progesterone production after intra amniotic injection of hypertonic saline (Luukkainen, cit by Csapo, 1961 b, Bengtsson & Stormby, 1962) It was known that saline induced abortions – i e the controls for these two hormone treated cases – were complete within 34 hours of saline injection (Bengtsson & Csapo, 1962) Thus a suppressive effect should be easily and rapidly detected

Case 1 J B 37 years physically healthy four children one abortion. Stage of pregnancy 19th week Intra amniotic recording before injection of hypertonic saline showed quite a normal picture (Fig 1, I) (*cf* Bengtsson & Csapo, 1962) After withdrawal of 160 ml amniotic fluid, 200 ml 20 % NaCl was injected intra-amniotically Sixteen hours later, intra amniotic recording showed the ordinary pronounced increase in myometrial activity (Fig 1, II A), the patient felt pains and the cervix was effaced in the upper parts but closed distally About 80 mg Provera (50 mg/ml) was injected at each of the three points mentioned above As the membranes were not ruptured, the needle was inserted into the amniotic cavity at each point (checked by aspiration of amniotic fluid) and then withdrawn Thus it could be assumed that most of the hormone was deposited in the myometrium. Two hours later, the contractions were subjectively less than before, and intra amniotic recording showed less tension during contraction (Fig 1 II B) During the following 12 hours the subjective pains completely disappeared Unfortunately, for technical reasons it was impossible to continue the intra amniotic recording External recording 13 hours after hormone treatment showed rather weak contractions with long intervals Fig 1, II C) Five days after saline injection there were still no pains An oxytocin drip was then started, but gave almost no subjective pains up to 60 mU Syntocinon/min After this fruitless treatment the patient was given œstrogen (ethinyl-œstradiol 0 5 mg) Next day the same oxytocin treatment was effective and she aborted in 6 hours *6 days* after saline injection

Case 2 H K 27 years, physically healthy, two children no abortion Stage of pregnancy 20th week After withdrawal of 200 ml amniotic fluid 190 ml saline was injected Eighteen hours after saline she had moderate pains and internal recording showed good contractions every 3 minutes (Fig 2 A) The upper part of the cervix was slightly dilated 250 mg Provera (50 mg/ml) was injected in three equal portions as in case 1 Three hours later internal recording showed weaker contractions with longer intervals (Fig

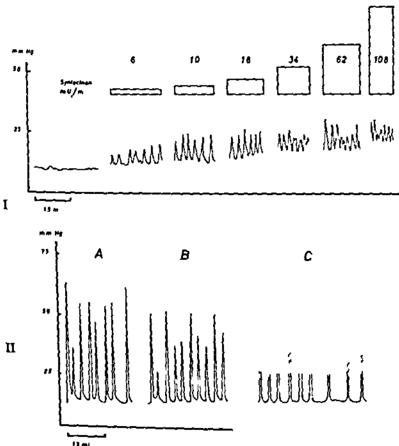


Fig 1 Case 1 saline induced abortion in the 19th week I spontaneous uterine activity and oxytocin sensitivity before saline injection II A spontaneous uterine activity 16 hours after saline injection B spontaneous uterine activity 2 hours after 250 mg Provera intra myometrially C spontaneous uterine activity 13 hours after 250 mg Provera intra myometrially

2 B) Her pains then disappeared completely Five days after saline injection there were still *no pains* Œstrogen (ethinyl-œstradiol 0 5 mg daily) and oxytocin (35 mU/min) were then given for two days and abortion occurred *6 days and 16 hours* after saline injection

It should be stressed that when uterine contractions have started after saline injection in control cases a spontaneous decrease has in no case been observed

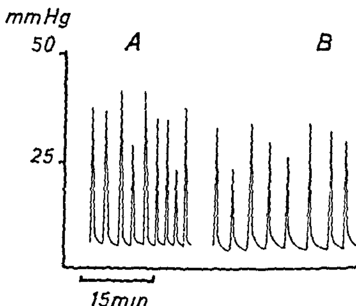


Fig 2 Case 2 saline induced abortion in the 20th week A uterine activity 18 hours after saline injection, B uterine activity 3 hours after 250 mg Provera intra myometrially

B *Spontaneous abortions*

Case 3 E W 30 years, one spontaneous abortion, no child Admitted to the hospital in the 20th week for ruptured membranes No subjective contractions, cervix normal closed Treatment bed rest, 250 mg Proluton depot (Schering) once weekly Piperidolati chloride (Dactil, Draco) 0 2 g daily Fourteen days after admission subjective pains began with rapidly increasing intensity and frequency down to a 7 minute interval The fœtal head was in the pelvic inlet and the cervix was dilated to 1 finger Two hundred and fifty mg Provera (50 mg/ml) was injected into the myometrium as described above After a temporary increase in the frequency and subjective strength of uterine contractions the activity began to decrease 2½ hours after hormone injection and had completely disappeared ¼ hour later During the following 6 days the patient was given daily intra myometrial injections of Provera in decreasing doses from 150 mg daily to 50 mg daily for the last two days During these 6 days she felt a few single painless contractions daily The Provera treatment was then interrupted and two days later the contractions increased in frequency and she had pains The amniotic fluid which flowed in increasing amount, was soon mixed with fresh blood The fœtal head and cervix were as before External tokometry (Fig 3, 1 A) showed well co-ordinated contractions every 5 minutes Two hundred and fifty mg Provera was injected intra myometrially Two hours later, the subjective contractions began to disappear Twelve hours after injection she felt

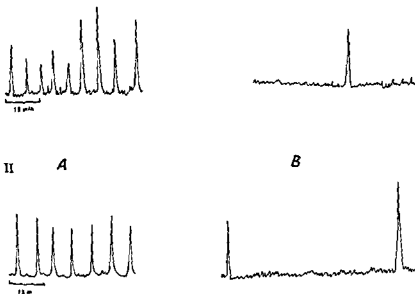


Fig 3 Case 3 spontaneous abortion in the 22nd week. I A uterine activity before treatment B uterine activity 12 hours after 250 mg Provera intra myometrially II A uterine activity after 2 days without treatment B uterine activity 12 hours after 250 mg Provera intra myometrically

no pains There was less blood in the amniotic fluid External recording showed one contraction in one hour (Fig 3 I B) No more Provera was given and two days later the pains and the bleeding reappeared The cervix was now fully effaced and the external os was open to one finger External recording showed contractions every 6 minutes (Fig 3 II A) 250 mg was again given into the myometrium as before Two hours later the pains were less External recording showed decreasing frequency Twelve hours after hormone injection there was one contraction per hour (Fig 3 II B) She was now in the 25th week of pregnancy and another 10 weeks would be required to obtain a viable child At the prospect of such long treatment which was of course rather painful further injections were refused Abortion occurred 3 days after the last hormone injection The fœtus died at the end of the abortion A careful *post mortem* examination showed no damages to the fœtus

Case 4 H C 31 years Two term deliveries Admitted to the hospital in the 18th week because of strong labour pains and bleeding Head in pelvic inlet Cervix fully dilated external os open to one finger External recording showed strong and co-ordinated contractions every 3 minutes (Fig 4 A) Four

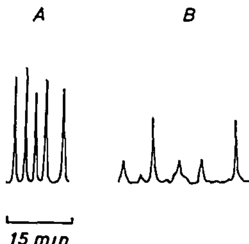


Fig 4 Case 4 spontaneous abortion in the 18th week. A, uterine activity before treatment B, uterine activity 3 hours after 400 mg Provera intra myometrically

hundred mg Provera (100 mg/ml) was injected into the myometrium Two hours after injection the pains began to decrease and one hour later were hardly perceptible External recording showed small contractions every 10 minutes and in between still smaller, inco-ordinated contractions (Fig 4 B) Further treatment was declined The pains reappeared next day, and the abortion was rapidly completed

C *Premature deliveries*

Case 5 K. L 30 years First pregnancy Admitted to the hospital in the 33rd week because of bleeding and weak pains Fœtal head in pelvic inlet Cervix dilated in the upper half, closed in the lower half External recording showed regular and co-ordinated contractions every 3 minutes (Fig 5 A) Four hundred mg Provera was injected (100 mg/ml) into the myometrium After a temporary increase the labour pains began to decrease 1 ½ hours after injection and then completely disappeared The treatment was continued by intra muscular injection in decreasing doses down to 100 mg Provera every second day External recording 5 days after the beginning of treatment showed small, irregular contractions which were completely painless (Fig 5 B) Ten days after the first injection there were only very small, inco-ordinated contractions as in normal pregnancy of the same stage (Fig 5 C) She delivered in the 37th week The child (2 600 g) was normal

Case 6 C J 24 years primigravida Admitted to the hospital in the 35th week because of labour pains Fœtal head in pelvic inlet Cervix not effaced but open to one finger External recording showed strong contractions every

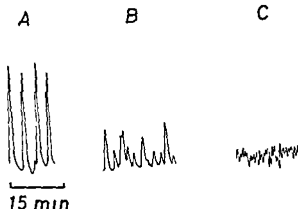


Fig 5 Case 5 Premature labour in the 33rd week A uterine activity before treatment B uterine activity after 5 days Provera treatment (see text) C uterine activity after 10 days Provera treatment (see text)

3 minutes (Fig 6 A) Two hundred and fifty mg Provera (50 mg/ml) was injected into the myometrium After 5 hours some irregularity (inco-ordination) was observed (Fig 6 B) otherwise no change Delivered 9 hours 20 min after injection The child died during delivery *Post mortem* examination showed severe malformations (gross umbilical herniation diaphragm defects malformed limbs)

Case 7 I L J 22 years One delivery at term two premature deliveries Admitted to the hospital in the 28th (32nd?) week because of ruptured membranes and bleeding Moderate pains every 2–3 minutes Fœtal head in pelvic inlet cervix partly effaced external os open to one finger Moderate bleeding External recording showed co-ordinated contractions every 2 minutes (Fig 7 A) Four hundred mg Provera (100 mg/ml) was injected into the myometrium as described above The subjective pains disappeared in a few hours Recording 24 hours later showed irregular (inco-ordinated) contractions completely painless (Fig 7 B) During the next 6 days she was given daily intra myometrial injections of Provera in decreasing doses down to 125 mg After that Provera was injected *intra muscularly* at first 200 mg daily and after some days 100 mg daily During these weeks she felt a few completely painless contractions every day Amniotic fluid drained continuously at first it was blood stained but after several days it was practically clear Twelve days after the first recording the uterine activity was recorded revealing one contraction in 30 minutes (Fig 7 C) After 3 weeks the treatment was changed to 100 mg Provera every second day Two and a half weeks later (5½ weeks after admission in the 33rd week of pregnancy) the pains started and rapidly strengthened No attempt was made to stop the

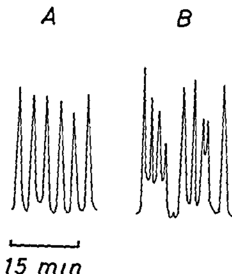


Fig 6 Case 6 Premature labour in the 35th week A, uterine activity before treatment B, uterine activity 5 hours after 250 mg Provera intra myometrially

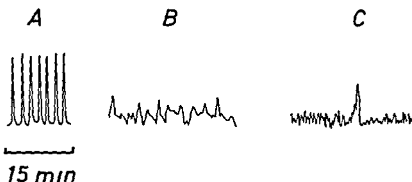


Fig 7 Case 7 Premature labour in the 28th (?) week A uterine activity before treatment B, uterine activity 24 hours after 400 mg Provera intra myometrially C, uterine activity after 12 days Provera treatment (see text)

contractions and the patient delivered in 17 hours The child (1 730 gm) survived and increased normally in weight

Case 8 U S 25 years One delivery at term no abortion Slight bleeding almost every day from the 8th week Admitted to the hospital in the 33rd week because of ruptured membranes and weak pains every 3-5 minutes The pains increased both in frequency and intensity, and external recording showed co-ordinated contractions every 3 minutes (Fig 8 I A) Fœtal head in pelvic inlet, cervix effaced in the upper half open to one finger in the

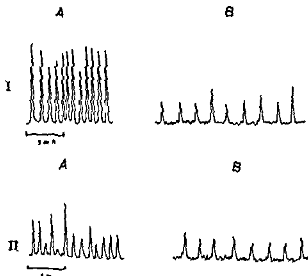


Fig 8 Case 8 Premature labour in the 33rd week I A uterine activity before treatment B uterine activity 12 hours after 150 mg Provera intra myometrially II A uterine activity after 2 days without treatment B uterine activity 12 hours after 250 mg Provera intra-myometrially

lower half One hundred and fifty mg Provera (50 mg/ml) was injected into the myometrium The pains disappeared after 3 hours and 12 hours after the hormone injection external recording showed weak contractions every 6–7 minutes (Fig 8 I B) No more hormone was given and she was without subjective pains for 48 hours The pains then reappeared and increased rapidly in strength and frequency After 2 hours *the cervix was fully effaced and the external os was open to almost 2 fingers* The head had begun to enter the pelvic cavity External recording showed well co-ordinated subjectively strong contractions every 3 minutes (Fig 8 II A) Two hundred and fifty mg Provera (50 mg ml) was given into the myometrium at three points in the anterior wall Twelve hours later she felt quite painless contractions external recording showed contractions every 6–7 minutes (Fig 8 II B) However the pains reappeared 20 hours after this Provera injection and increased very rapidly Delivery was completed in 1 ½ hour before further treatment could be given

Case 9 M S 22 years One delivery at term one premature delivery Admitted to the hospital in the 35th week for ruptured membranes and mild pains Foetal head in pelvic inlet Cervix fully effaced External os open to one finger External recording showed co-ordinated contractions with 5–6 minutes intervals (Fig 9 A) Two hundred and fifty mg Provera (50 mg ml)

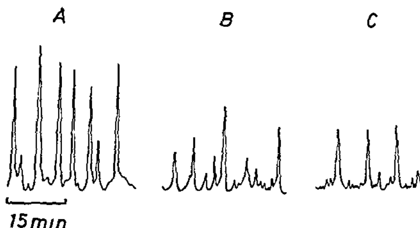


Fig 9 Case 9 Premature labour in the 35th (?) week A, uterine activity before treatment, B, uterine activity 16 hours after 250 mg Provera intramyometrially, C, uterine activity 24 hours after 250 mg Provera intramyometrically

was injected into the anterior uterine wall Four hours later she felt no pains Sixteen and 24 hours after injection respectively, external recording showed contractions every 9 minutes, which were not perceived by the patient (Fig 9 B and C) Forty-eight hours after the hormone injection she felt the contractions once more The fœtal head had then begun to enter the pelvic cavity, the cervix was fully effaced as before and the external os was open to almost 2 fingers Two hundred mg Provera was again given into the myometrium Sixteen hours after the last injection the pains rapidly increased She delivered in 2 ½ hours before further treatment could be tried The weight of the normal child was 2 880 gms Thus, the patient was possibly closer to term than was calculated

Case 10 B A 22 years One delivery at term, no abortion Admitted to the hospital in the 33rd week because of ruptured membranes pains and bleeding Fœtal head in the pelvic inlet, cervix fully effaced and the external os open to one finger External recordings showed mainly co-ordinated contractions with 2-3 minutes intervals (Fig 10 A) Three hundred mg Provera (100 mg/ml) was injected into the anterior uterine wall Next day the contractions were somewhat less regular but otherwise there was no change Therefore 400 mg Provera was injected into the myometrium. Next day she felt no contractions at all and external recording showed contractions with about 6 minutes intervals (Fig 10 B) But on the following day the pains reappeared, and she delivered in 3 ½ hours in spite of 200 mg Provera intra myometrially The child (1,640 gms) had multiple malformations in the heart, aorta, œsophagus, arms and hands and died after operation for atresia of the œsophagus

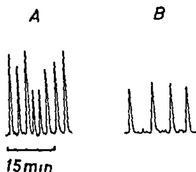


Fig 10 Case 10 Premature delivery in the 33rd week A uterine activity before treatment B uterine activity after 2 days Provera treatment (see text)

Case 11 J S 25 years First pregnancy Admitted to the hospital in the 34th week because of ruptured membranes, pains and bleeding Fœtal head in pelvic inlet Cervix fully dilated and open to 2 fingers External recording showed strong contractions every 4 minutes Four hundred mg Provera was injected into the myometrium (100 mg/ml) No effect was observed and she delivered 9 hours later The child was normal

Case 12 I J 29 years First pregnancy Admitted to the hospital in the 32nd week because of ruptured membranes and strong pains Fœtal head in pelvic cavity Cervix fully dilated and external os open to one finger External recording showed strong and regular contractions every 3–4 minutes (Fig 11 A) Three hundred and seventy five mg Provera (100 mg/ml) was injected into the myometrium Four hours later she felt the pains somewhat less and external recording showed some inco-ordination of contractions (Fig 11 B) However the pains again increased in strength and she delivered 12 hours after injection. (Twins 1 880 gms and 1 430 gms respectively)

Case 13 G S 22 years First pregnancy Admitted to the hospital in the 35th (39th?) week because of strong labour pains Fœtal head in pelvic cavity Cervix fully effaced external os open to 2 fingers External recording showed strong contractions every 4 minutes Two hundred and fifty mg Provera (50 mg/ml) was injected into the myometrium. No effect was observed and the patient delivered 2 hours after injection (Normal child weight 2 650 gms)

Case 14 M B T 18 years First pregnancy Admitted to the hospital in the 29th week because of strong labour pains Fœtal head in the pelvic cavity cervix effaced external os open to two fingers 250 mg Provera was injected into the myometrium This had no effect and the woman delivered 1 hour after injection

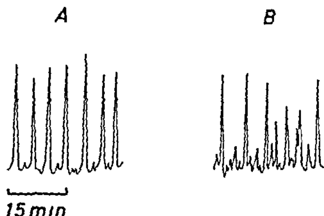


Fig 11 Case 12 Premature delivery in the 32nd week A, uterine activity before treatment B, uterine activity 4 hours after 375 mg Provera intra-myometrially

As is evident from Table 1, intra-myometrial injection of Provera suppressed effective uterine contractions in 9 out of 10 cases when the fœtal head was in the pelvic inlet and the external os was open to not more than one finger If the fœtal head had entered the pelvic cavity, Provera treatment was ineffective In such cases (No 12-14) the delivery was rapidly completed In one case (No 11) the head was still in the pelvic inlet, but the external os was open to more than one finger (cervix fully effaced), and Provera treatment had no effect The only case which responded very little (inco-ordination of contractions) to Provera treatment in spite of a favourable condition (fœtal head in pelvic inlet, cervix closed) was No 6 This patient delivered a child with severe malformations

Discussion

The investigation indicates that if a gestagen (Provera) is given so as to produce a high concentration in the myometrium, myometrial activity is suppressed It should be noted that the series covers the period from the 18th to the 35th week of gestation

It may be suggested that any inert substance injected into the myometrium might have a similar inhibiting effect and that the gestagen might have a local anaesthetic effect From a theoretical point of view, however, this is improbable, because every inter

ference with the pregnant myometrium has a stimulating and not an inhibiting effect Also Provera, injected into the myometrium, in some instances showed a temporary stimulating effect before the suppression As a control observation a local anæsthetic (1 5 ml 1 % Xylocain) was given at each of the three points of the myometrium in a case of saline induced abortion in the 20th week This case was carefully selected and treated so as to resemble closely the two legal abortions described above The local anæsthetic had no effect the woman aborted 37 hours after saline injection It has been reported by Theobald (1961) that oil, injected into the myometrium, has no inhibiting effect It is most improbable therefore that intra myometrial injections of inert substances should have a suppressing and pregnancy-pro longing effect or that Provera should act as a local anæsthetic

Many problems concerning this method of suppressing uterine activity are unsolved but under investigation how often threa tened abortion and premature labour can be supported to a stage where the fœtus has a reasonable chance of survival, the lowest effective dose in different stages of pregnancy, whether intra myometrial injections of Provera, after having suppressed my-ometrial activity can be replaced by intra muscular injections or by oral treatment of the same substance, and whether intra myometrial injections of progesterone have the same inhibiting effect Many problems therefore, remain to be solved before we can judge the clinical value of this treatment It should be stres ed that the aim of this investigation was purely experimen tal to check the validity of the theory that gestagens are effective if given so as to produce a high concentration in the myometrium In some later cases, however, gestation was prolonged until the child was viable

As the experiments were performed only in cases where spon taneous decrease in myometrial activity is never observed (saline induced legal abortions) or only rarely observed (inevitable

Since this paper was written it has come to my notice that comparable *results have been obtained by Dr E.* Coutinho Bahia by injection of progesterone into the myometrium through the anterior fornix of the vagina Similar conclusions are drawn from both sets of experiments with regard to the hormonal control of the myometrium of the pregnant human uterus

abortion and inevitable premature delivery), the results appear to be significant even without controls

The results indicate that gestagens are key substances in the maintenance and termination of human pregnancy

SUMMARY

Based on the theory that if an effective gestagen is applied so as to produce a high concentration in the myometrium, it ought to be effective in all stages of pregnancy, a potent gestagen, Provera (Upjohn) was injected directly into the myometrium through the abdominal wall in 2 cases of saline induced therapeutic abortion, 2 cases of 'inevitable' spontaneous abortion and 10 cases of 'inevitable' premature delivery The effect of this treatment, studied by recording the uterine activity, could be related to the degree of progress in labour if the fœtal head was in the pelvic inlet and the external os was open to a maximum of one finger, the myometrial activity was suppressed in 9 out of 10 cases If the fœtal head had entered the pelvic cavity, the treatment was ineffective

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PLACENTAL TRANSFER OF FLUORINE INVESTIGATED WITH F^{18} IN MAN AND RABBIT

BY

Y ERICSSON AND CL MALMNÄS

Studies on the placental transfer of fluorine have been motivated especially by the discoveries of the influence of fluorine on the mineralization of the teeth and their resistance to dental caries, and by the skeletal changes following high doses of fluorine A thorough knowledge of this aspect of the physiology of fluorine is of importance both from a general toxicologic point of view and because the mineralisation of both skeleton and teeth begins during fœtal life

Most previous investigations on the transfer of fluorine across the placenta have been performed in animals Knouff *et al* (1936) demonstrated the presence of fluorine in the fœtuses of dogs that had drunk water containing 25 mg fluorine per litre but not of dogs whose drinking water contained only 5 mg/l (5 ppm) Murray reported in the same year that the offspring of rats given 50 ppm fluorine in their solid food showed a fluorine content of 5 1 ppm, while the offspring of control animals without fluorine addition to their diet contained 1 1 ppm F

Evans and Phillips (1939) demonstrated the transfer of fluorine across the placentæ of rats, but no increase in the fœtal fluorine content could be detected until the dams obtained 10 ppm F in milk (which with the addition of certain salts com

prised their total diet) Lehman and Muhler (1954) reported a relationship between the fluorine supply to pregnant rats and the fluorine content of their offspring Suttie, Miller and Phillips (1957) were able to measure fluoride transfer across the cow s placenta

Minoguchi and Iwamoto (1957) investigated the fluorine content of different organs and tissues in new-born dogs puppies whose mothers had obtained I 30 mg NaF in their daily ration for one year, II the same dose for 2 months of pregnancy, III no addition of fluorine Compared with the puppies of the control animals the puppies of the animals in Group II showed an increase of the fluorine content of different bones amounting to 15–100 per cent and in the teeth about 100 per cent The corresponding increase in the puppies of Group I was about 4–7 fold in bones and about 8 fold in the teeth Büttner and Muhler (1958) reported that drinking water containing 10 ppm F must be given to pregnant rats in order to obtain a measurable increase of the fluorine content of the fœtal skeletons With 50 ppm F in the rats drinking water during pregnancy the fœtal fluorine content was about trebled

Ericsson and Ullberg (1958) demonstrated autoradiographically with F^{18} that this fluorine isotope was taken up to a considerable extent by the placentæ of mice and especially by the degenerative calcium salt precipitations that often occur during the later part of the pregnancy The small quantity of F^{18} that passed into the fœtuses was mainly concentrated in the mineralized parts of the fœtal skeletons Cohen (1959) demonstrated qualitatively a transfer of F^{18} through the rat s placenta within one hour after intravenous injection Maplesden *et al* (1960) in the full term fœtuses of rats on greatly varying fluoride intake found a fluorine content which corresponded to about 1 per cent of the concentration in the dams Rabbit fœtuses contained about 2–3 times as much fluorine under the corresponding experimental conditions

In man relatively few and incomplete investigations into the placental transfer of fluorine have been performed Held (1952) found about the same fluorine content in the umbilical cord blood at parturition as in the mother s blood Feltman and Kosel

(1955) analysed the fluorine content of the placenta and the umbilical-cord blood at birth Following the ingestion of fluorine in optimal caries-preventive dosage, either as tablets or in drinking water, 10–30 per cent more fluorine was detected in the placenta and about 100 per cent more in the umbilical-cord blood than was found in the control cases Gardner *et al* (1952) also found many times more fluorine in the placenta than in the maternal blood at the time of delivery

Brzezinski *et al* (1960) found 13 0 mg F/100 g femur in 9-month fœtuses in Jerusalem (0 55 ppm F in the drinking water) a figure which is less than 1/3 of the normal fluorine content in the bones of adults

Owing to the difficulties inherent in the chemical analysis of low fluorine concentrations in organic material one must accept the possiblity of large errors in the analytical figures given above, especially in the older figures The quoted investigations have, however, shown a limited and apparently variable permeability of the placentae to fluorine in the species investigated

Purpose of the present investigation

The short half-life and relatively high permissible body dose of F^{18} (about 110 minutes and about 20 μc, respectively, Armstrong *et al*, 1958, Morgan, 1954) made possible a short term kinetic study of the fluoride transfer across the placenta of certain patients undergoing therapeutic abortions by Cl Malmnäs, using F^{18} prepared according to Y Ericssons technique Owing to the stringent indications for these experiments that were adopted for safety reasons (see below), the number of patients available for study was, however very limited The investigations were therefore supplemented with experiments on rabbits, whose placentae are of the same main type as that of the human The existence of several fœtuses in the rabbit makes it possible to some extent to study the placental transfer longitudinally by removing the fœtuses at varying intervals

In addition in the rabbit experiments as many determinations as possible were performed on the F^{18}-uptake of mammary glands, thyroid and hypophysis These were limited by the necessity for

rapid work because of the short half life of the isotope These organs have attracted a certain interest in connection with fluoride metabolism

Production of F^{18} Radiometric methods

F^{18} was produced in the Stockholm uranium reactor and purified by distillation according to previously described principles (Ericsson and Ullberg 1958) Co distillation of chloride and perchlorate ions, the latter being toxic because of methæmoglobin formation, was prevented or reduced by the addition of silver perchlorate and sodium perchlorate, respectively, to the distillation vessel (Armstrong 1936 a, b) 10 ml distillate was received in 1 ml 0 5 N NaOH The pH value of the distillate was adjusted to 6–7 5 and NaCl was added to bring the solution to approximately physiological ionic strength After preliminary determination of the activity on a small sample in known dilution the F^{18}-distillate was sterilized for the human experiments by boiling in a stoppered hard glass tube in a water bath

All samples of blood and tissues were weighed in plastic tubes containing a small drop of heparin and were then diluted to a 2 ml level marked on the tubes Samples of the F^{18} solutions for injection were diluted in the same way Analysis was performed with a scintillation counter with a well type crystal, into which the plastic tubes fitted exactly The applied geometry had been evaluated previously (Ericsson *et al* 1961) The radiometric errors were as follows

Human experiments		
maternal blood and placenta	about	1 – 2 5 %
fœtal blood		6 – 7 %
Rabbit experiments		
maternal blood	about	0 5 %
fœtal blood		1 %
mammary glands		1 %
thyroid		1 5 %
hypophysis		2 5–10 %

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The short half-life and relatively high permissible body dose of F^{18} (about 110 minutes and about 20 μc, respectively, Armstrong *et al*, 1958, Morgan, 1954) made possible a short term kinetic study of the fluoride transfer across the placenta of certain patients undergoing therapeutic abortions by Cl Malmnäs, using F^{18} prepared according to Y Ericsson's technique Owing to the stringent indications for these experiments that were adopted for safety reasons (see below), the number of patients available for study was, however very limited The investigations were therefore supplemented with experiments on rabbits, whose placentæ are of the same main type as that of the human The existence of several fœtuses in the rabbit makes it possible to some extent to study the placental transfer longitudinally by removing the fœtuses at varying intervals

In addition in the rabbit experiments as many determinations as possible were performed on the F^{18} uptake of mammary glands, thyroid and hypophysis These were limited by the necessity for

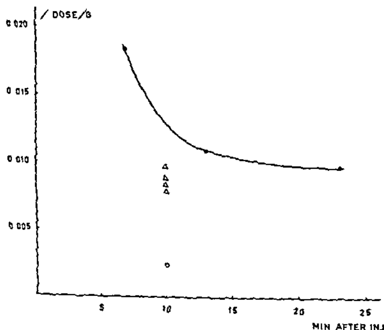
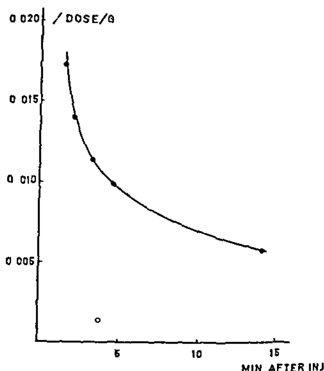


Fig 2 Mother H J 35 years heart disease gravida V para II Fœtus 12 cm

old girl who was physically healthy In the other cases the indications for operation were mainly somatic and the patients had previously had one or more normal pregnancies

All operations were performed under general anæsthesia with pentothal curare and ether Abdominal hysterotomy was performed in all cases and the removal of fœtus and placenta was carried out with as little tissue damage as possible

F^{18} was injected intravenously in one of the patient s arms and blood samples were taken through a heparinized needle from the other arm Blood from the fœtus was taken from the umbilical cord and/or the heart In three of the cases tissue samples were taken from different parts of the placenta for F^{18}-determination The times of the F^{18} injection and the taking of each sample were noted exactly in order to correct for radio-active decay



Figs 1–4 *Human experiments* F^{18} content of maternal blood (●), fœtal blood (○) and placenta (△)

Fig 1 Mother A B, 18 years, mental deficiency, gravida I Fœtus 26 cm

Experiments on man

For the human experiments the lowest F^{18}-dosage was used that could be expected to give a measurable activity in about 1 ml fœtal blood counted as soon as possible after drawing the sample (hence the greater error in the human experiments) The injected dose was about 5 μc, which is far below the accepted maximal dose

Since genetic damage by injected radio-active isotopes cannot be completely excluded, the experiments with F^{18} were performed only in cases where therapeutic abortion was to be combined with sterilization The age of the subjects, indications for operation and fœtal size are shown in the legends of figs 1–4 The youngest patient was a seriously mentally defective 18 year

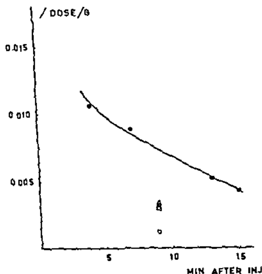


Fig 4 Mother S A 39 years heart disease gravida VIII para III Fœtus 15 cm.

cannula was inserted in one of the carotid arteries After these preparations 8–10 uc F^{18} per kg body weight was injected intra venously

Samples of the maternal blood were drawn through the carotid cannula before the intravenous injection of F^{18} and repeatedly, with 2–5 minute intervals, after the injection

The fœtuses were removed in sequence during a 35 minute period following the injection of F^{18} A longer experimental period would have involved considerable risks of sudden abortion, to judge from previous experience and from the incipient uterine contractions during the experiment. The fœtal membranes and the placenta were removed and blood was drawn from the heart of the fœtus

In some of the experiments mammary glands of the dam from which milk could be expressed, were excised

After removal of all the fœtuses the dam was killed by rapid bleeding or intra arterial injection of air The thyroid and hypo physis were taken out the latter from the cranial side after re

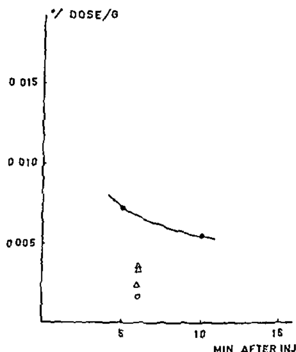


Fig 3 Mother M F, 36 years, diabetes mellitus + prurigo gestationis of Besnier, gravida II, para I Fœtus 15 cm

Results

The results are shown in figs 1–4

The F^{18} was evidently rapidly eliminated from the maternal blood The F^{18} content of the fœtal blood was consistently much lower, varying between 1/4 and 1/10 of that of the maternal blood The F^{18} content of the placenta was between those of the maternal and fœtal blood

Rabbit experiments

For the rabbit experiments animals were used which had been mated 29 days previously and thus had only 2 days left before expected parturition The animals were anæsthetized by slow intravenous injection of about 5 ml 25 % urethane solution per kg bodyweight Tracheotomy was performed, and a heparinized

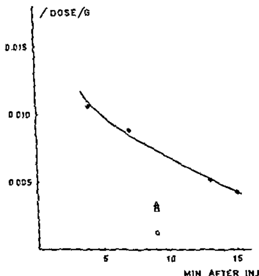


Fig 4 Mother S A 39 years heart disease gravida VIII, para III Fœtus 15 cm

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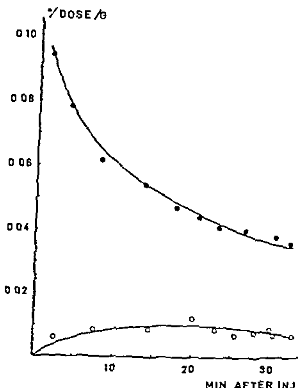


Fig 5

Figs 5–7 *Rabbit experiments* F^{18} content of maternal blood (●) and fœtal blood (○) after 29 days pregnancy Weights of animals Fig 5 4 46 kg, Fig 6 3 55 kg Fig 7 4 17 kg

moving parts of the skull and the brain Sampling time for thyroid and hypophysis was regarded as coinciding with the time of death of the animal and cessation of the circulation

Results

The results for the placental transfer in the rabbits are summarized in the diagrams figs 5–7

The F^{18} activities of the hypophysis, thyroid and mammary glands appear in Table I

As expected, the decrease of the F^{18} content of the maternal blood is very rapid The F^{18} transfer to the fœtal blood is very limited and shows only a slight increase during the 30–35 minutes

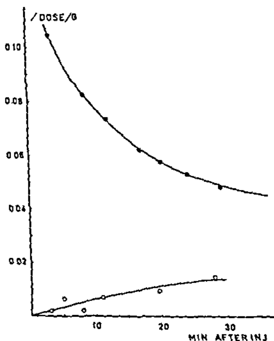

/ DOSE/G
0.10
0.08
0.06
0.04
0.02
10
20
30
MIN AFTER INJ

Fig 6

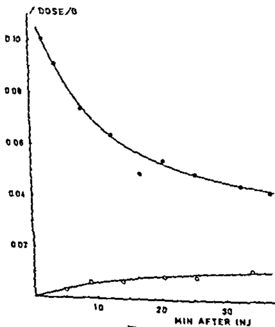

/ DOSE/G
0.10
0.08
0.06
0.04
0.02
10
20
30
MIN AFTER INJ

Fig 7

Table I F^{18} *Activity of Thyroid, Pituitary and Mammary Glands Compared with Activity of the Blood*

	Animal 1		Animal 2		Animal 3	
	Time after Inj Min	% of Dose	Time after Inj Min	% of Dose	Time after Inj, Min	% of Dose
Maternal blood		0 037		0 048		0 0[illegible]
Thyroid	35 5	0 013	35	0 051	38	0 023
Pituitary		0 046		0 076		0 0[illegible]3
Maternal blood			15	0 066	19	0 058
Mammary gland				0 027		0 0[illegible]4

of the experiments, in one of the experiments an apparent decrease is observed after 20 minutes In no case does the fœtal blood concentration reach 1/3 of the simultaneous F^{18} concentration in the maternal blood

The F^{18} activities of the hypophysis and thyroid are of the same order as that of the blood (The somewhat higher hypophysis activity found in one of the animals may, according to an observation by one of the participating personnel, have been due to a small accompanying bone-chip, in spite of the great care taken to avoid this obvious source of error)

The F^{18} content of the mammary glands is in both cases tested considerably lower than the simultaneous content of the blood

Discussion

The disappearance curves for F^{18} in human and rabbit maternal blood are in fair agreement with previously found values for rats weighing about 200 g (Wallace-Durbin, 1954), if allowance is made for the different bodyweights of the species In these rats the blood F^{18} concentration 15 minutes after intravenous injection was about 0 5 % of the dose per gram while our values after the same time were 0 05–0 07 %/g for rabbits and 0 004–0 01 %/g for humans

While it has been shown in previous investigations on different species that the placenta forms a partial barrier to fluorine, the data presented here demonstrate that even sudden increases of

the fluoride concentration of the maternal blood cannot produce any great rises in the concentration in the fœtal blood In addition to this the fluorine content of the maternal blood shows very little increase even following excessive peroral ingestion (Wallace Durbin, 1954, Ericsson, 1957) For example, Ericsson found that the maximum concentration of F^{18} in the blood of adult rats following peroral ingestion as an aqueous solution on a fasting stomach was about 0 18 % of the dose per ml blood The dose given to these rats was dissolved in 10 ml NaF solution containing 1 mg F per litre, and the uptake of inactive fluorine in the blood that corresponded to its F^{18} concentration was about 0 02 mg/l or less than 10 per cent of the normal fluorine content of rats blood In proportion to the bodyweight the corresponding peroral dose to a woman weighing 64 kg would be 2 litres of water containing 2 mg fluorine The fœtuses are thus well protected against any toxic action of fluorine

It is of interest to compare the fluorine transfer through the placenta with the corresponding transfer of other ions which have been studied with the aid of radioactive isotopes (reviews Sternberg 1960 Hagerman and Villee, 1960) While *e g* the placental transfer of calcium, radium and plutonium has been shown to decrease with increasing atomic weight (Plumlee *et al* 1952 Wilkinson and Hoecker, 1953) the reverse seems to be the case with the halogens Iodine is thus accumulated in the fœtus (Logothetopoulos and Scott, 1956, Lybeck and Hirvonen 1956 *et al*) bromine is accumulated in certain fœtal tissues (Soremark, 1960 Soremark and Ullberg 1960) the chlorine concentration seems to be about the same in fœtal blood as in maternal blood (Needham, 1931) and the fluoride transfer is according to this and previous investigations very limited

It is also of interest in this connection that the transfer of the different halogens across the gastric mucosa seems to follow the same order (iodine bromine chlorine fluorine) as the placental transfer (review Soremark 1960 Ullberg and Soremark, 1961) Possible theoretical explanations of these conditions will not be discussed here

At the fœtal maturities investigated by us there was no fluoride

accumulation in human placenta in contrast to the observations at parturition by Gardner *et al* (1952) and Feltman and Kosel (1955) Even if the simultaneous analyses by these authors of maternal and umbilical cord blood do not agree with later results obtained with improved methods, it seems probable that fluoride accumulation in the placenta takes place towards the end of the pregnancy, according to the autoradiographic observations of F^{18} uptake in calcifications in the placenta, which have been done by Ericsson and Ullberg (1958) on full term mice, it seems probable that it is these calcifications, common during the later period of pregnancy, which cause the fluoride uptake

Our determinations of the F^{18} uptake by the rabbit pituitary contradict Bazille's analytical figures (1935), according to which the pituitary of the rabbit takes up even more fluorine than the bone

The thyroid has previously been suspected of accumulating halogens other than iodine, among them fluorine This has been contradicted by previous F^{18} investigations (Wallace-Durbin, 1954, Ericsson and Ullberg, 1958) and evidently also by the data presented here

It is well known that variations of the fluoride intake have little or no influence on the fluoride content of the milk Neither does any concentration seem to occur in the mammary tissue proper according to our analyses This is in agreement with Wallace Durbin's results

SUMMARY

A review of the literature summarizes the results of previous investigations on the placental transfer of fluoride in experimental animals and humans

The fluoride transfer across the placenta was studied with the aid of radioactive fluorine in four human cases of therapeutic abortion and sterilization and in 3 rabbits in late pregnancy

In humans the F^{18} concentration of the fœtal blood never exceeded 1/4 of the simultaneous concentration in the maternal blood during observation periods up to 10 minutes after intra venous injection of F^{18} In the rabbits, where the fœtuses were

removed successively up to 35 minutes after intravenous injection of F^{18}, the corresponding maximal figure was 1/3 of the concentration of the maternal blood In the human placenta the F^{18} concentrations lay between those of the maternal and fœtal blood No rapid accumulation was thus found in the placenta at these stages of development (12–15 cm fœtal length)

In the rabbit experiments the F^{18} concentrations were also analysed in the thyroid and pituitary 35–38 minutes after the injection and in the mammary glands 15–19 minutes after the injection, and compared with the simultaneous concentration in the maternal blood The F^{18} content of these tissues was of the same order as, or lower than, that of the maternal blood.

The results are discussed with special regard to possible conclusions concerning the protection of the fœtus against overdosage of fluorine, and comparisons are made with the permeability of the placenta for other ions, in the first rank the halogens

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OXYTOCIN TREATMENT DURING THE ESTABLISHMENT OF LACTATION

BY

MOGENS INGERSLEV AND KIRSTEN PINHOLT

In 1910 Ott and Scott demonstrated in animal experiments that extracts from the posterior pituitary exerted an influence on the lactiferous glands. These observations were further substantiated and supplemented during the next few decades, but it was only after synthetic production of oxytocin (du Vigneaud *et al.* 1953) and subsequent elaboration of methods of standardisation in experiments on lactating rabbits (Berde 1959, Berde and Cerletti 1960) that extensive studies were performed on the effect of oxytocin on the mammary glands. It is now clear that oxytocin exerts an action on the myo-epithelial elements of the duct system by which it induces or promotes the flow of secretion from the alveoli. Under physiological conditions, this milk let-down reflex is excited by liberation of oxytocin from the neurohypophysis mainly through neural impulses generated from the nipple during the process of suckling. On the other hand, it is doubtful whether oxytocin exerts a direct influence on the process of secretion.

The literature on the influence of oxytocin on the mammary glands is chiefly concerned with the effect of intramuscular administration of the drug. However, during recent years special attention has been focused on experiments in which oxytocin is applied to the nasal mucosa, since this route of administration also leads to rapid absorption; this method has been used both in the

stimulation of uterine contractions to accelerate delivery and in the treatment of lactation disturbances

A considerable body of literature on the effect of oxytocin during the establishment of lactation is now available A number of investigators obtained good results irrespective of the mode, dosage, and other factors of administration However, owing to variations in the experimental conditions it is hardly possible to compare the results of these studies, and it is not immediately apparent why oxytocin was without effect in some of the experiments

The criteria adopted in assessing the effect of oxytocin differ in the various reports It seems to be easiest to assess the results of the investigations from measurements of the amounts of milk withdrawn from the breast at individual feed (Newton and Newton, 1951, Hæger and Jacobsohn, 1953, Newton and Egli, 1958, Baumgarten and Hofhansl, 1959, Baumgarten and Watzek, 1959, Hollenbach, 1959, Jensen, 1959, Wenner, 1959, Thorsøe, 1960, Kullander, 1960), since most of these reports contain suitable control series There is little doubt that oxytocin treatment results in an increase in the amount of milk withdrawn at individual feed, but from this observation it can only be concluded that the emptying of the acini and the system of lactiferous ducts under the conditions studied is more effective than a preceding of subsequent feed without oxytocin stimulation It cannot be concluded from this that the total milk production over 24 hours or even a longer period is increased

The influence of oxytocin has also been assessed on the basis of the extent and duration of engorgement of the breast (Newton and Newton, 1951, Hæger and Jacobsohn, 1953, Ingelmann-Sundberg, 1953, Baumgarten and Hofhansl, 1959, Baumgarten and Watzek, 1959, Hollenbach, 1959, Jensen, 1959, Wenner, 1959, Whitelaw *et al*, 1959, Thorsøe, 1960) Most of these publications have no control series Moreover, they disregard the fact that the course of breast engorgement differs in primiparae and multiparae, and that this engorgement is a condition which passes off spontaneously and shows considerable variation in duration and severity

In the reports in which the frequency of breast infection was

used as a criterion control series are also missing (Baumgarten and Watzek, 1959, Hollenbach, 1959, Jensen, 1959, Wenner, 1959) In this connection it must be emphasised that a number of factors related to the establishment of lactation are greatly influenced by the interest shown by the nursing mother and the hospital staff

Clinical Material and Technique

Studies of the literature show that nasal application is the only form of administration which is suitable for large scale experiments At the same time it is imperative that the clinical experiments are designed so as to include a reliable control series in order to rule out the possiblity that the results obtained can be attributed merely to the experiment In addition, it is desirable that as many criteria as possible are included, and that the series is so large that it can be divided into appropriate subgroups, for example, according to parity and birth weight

Synthetic oxytocin was administered from a spray bottle Immediately before each breast feed the patient applied a dose of about 4 I U to the mucosa of one nostril This treatment, was continued until lactation had been established, *i e* until the infant had regained its birth weight, or until at least the eight day *post partum* The control series was obtained as follows one half of the spray bottles used contained oxytocin and the other half a placebo At the conclusion of the experiment the manufacturer submitted a code by which it was possible to determine whether the bottles used by the individual patients had contained oxytocin or placebo

The experimental series comprised 500 cases, *viz* all puerperal women in the maternity hospital during a given period, with the exception of mothers with still born babies, mothers whose babies died within the first 24 hours after birth, or whose babies were to be adopted and mothers who had been admitted to the maternity hospital from their homes or from other hospitals later than 24 hours after delivery When the code was disclosed we had

[1] The spray bottles containing oxytocin (Syntocinon) or placebo for experimental use were generously supplied by Sandoz A. G Basle Switzerland.

two groups, each consisting of 250 mothers treated with either oxytocin or placebo Before the analysis of the results, five mothers of twins from each of the two groups and three other mothers whose babies died on the second day after delivery were excluded, the oxytocin group then consisted of 243 and the placebo group of 244 patients

A closer analysis of the two groups showed that they were of uniform composition regarding a number of the factors which are of decisive importance in the establishment of lactation

As will be seen from Table I, the distribution of the mothers according to age and parity was almost identical in the two groups

Table I *Distribution of the Mothers According to Age and Parity, and of the Infants According to Birth Weight*

	Oxytocin Group	Placebo Group
Age of the mothers, in years		
−20	56	57
21–30	126	129
31–40	56	53
41–	5	5
Parity		
Primiparæ	123	133
Secundiparæ	63	61
Multiparæ	57	50
Birth weight of infants in grammes		
< 2 500	19	17
2,500–2 950	52	37
≥ 3 000	172	190

The frequency of complications in the two groups was also similar Thus, for example, Rhesus immunisation was encountered in 22 babies in each of the two groups, and Cæsarean section was performed in 12 cases in the oxytocin group and in 9 in the placebo group

During the experimental period we adhered to our usual routine employed in the establishment of lactation The babies were put to both breasts four hourly throughout the day until the engorgement had disappeared After each feed residual milk was expressed manually from the breast to ensure complete emptying When the engorgement diminished, the baby was put to only one breast if there was sufficient milk If the slightest sign of a nipple fissure appeared the baby was taken from the breast, which was then emptied manually for one or two days until the nipple had healed Cases with a tendency to excessive engorgement were given œstrogen treatment When it was suspected that breast feeding was inadequate, the baby was weighed before and after each feed for 24 hours, and the amounts of milk expressed from the breasts were also weighed A supplementary artificial feed was given when this seemed necessary as assessed by the baby s weight (measured every second day) and reactions A lactation record with all relevant factors was kept for each mother These records formed the basis for our subsequent analysis of the results

Results

The purpose of the present investigation was to clarify the value of nasal application of oxytocin in the aforementioned dosage during the establishment of lactation The criteria chosen for the assessment of the effect obtained were (1) the milk production estimated as a fraction of the baby s total food intake and the rate of weight gain and (2) the frequency of lactation disturbances during the establishment of lactation

Based on a division of the series according to the babies total food intake during the first week of life it was found that 78 per cent (or 189) of the babies in the oxytocin group were fed on breast milk alone as compared with 81 per cent (or 197) of the babies in the control group The corresponding figures in the two groups for babies who were given breast milk with a supplementary feed amounting to less than 50 per cent of the total food intake were 12 and 10 per cent and for babies given breast milk *with a supplementary* feed of more than 50 per cent of the total food intake 10 and 9 per cent, respectively

two groups, each consisting of 250 mothers treated with either oxytocin or placebo Before the analysis of the results, five mothers of twins from each of the two groups and three other mothers whose babies died on the second day after delivery were excluded, the oxytocin group then consisted of 243 and the placebo group of 244 patients

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Although these subjective factors must be borne in mind, uncertainty is lessened by the fact that neither the doctors nor the nurses knew whether a given patient had received oxytocin or placebo during the experiment (Table III)

Table III *Frequencies of Engorgement and of Fissures and Epithelial Lesions in the Oxytocin and Placebo Groups Observed in the Entire Series and in the Subgroups of Primiparæ and Multiparæ*

	Entire Series				Primiparæ				Multiparæ			
	Oxytocin 243		Placebo 244		Oxytocin 126		Placebo 133		Oxytocin 117		Placebo 111	
	No	%	No.		No.		No	%	No		No	
	141	59	163	67	72	57	92	69	69	59	71	65
sures and epithelial lesions	25	10	25	10	14	11	14	10 5	11	9 4	11	10

It appears from Table III that engorgement of the breast was less frequent among the patients treated with oxytocin than among those in the control group However, subdivision of the series into primiparæ and multiparæ revealed that this difference was mainly due to the fact that the engorgement was appreciably less frequent in primiparæ having oxytocin treatment than in primiparæ in the control group The difference in the two groups of primiparæ amounts to twice the standard error and is thus statistically significant This observation is in agreement with the fact that engorgement required treatment with œstrogens in 21 per cent of the patients in the oxytocin group as compared with 25 per cent in the control group

The frequency of epithelial lesions and fissures was identical in the two groups both in the series as a whole and in the subgroups of primiparæ and multiparæ Two cases of galactophoritis were noted in each group whereas mastitis did not occur

Discussion

Many observations are in favour of the assumption that both early cessation of lactation and inadequate milk production must

Further subdivision of the series according to the age and parity of the mothers and the birth weight of the babies revealed that the distribution of the babies from the oxytocin group and the control group was almost identical However, it must be emphasised that 68 per cent of the infants with a birth weight below 2,500 g in the oxytocin group managed on breast milk alone as against only 47 per cent of the smaller babies in the control group (Table II)

Table II *Distribution of the Infants from the Oxytocin and Placebo Groups According to Birth Weight and the Type of Feeding*

Type of Feeding	Birth Weight below 2,500 g				Birth Weight 2,500–2,950 g				Birth Weight [illegible]		
	Oxytocin		Placebo		Oxytocin		Placebo		Oxytocin		Placebo
	No	%	No.	%	No	%	No.	%	No.		No
reast milk	13	68	8	47	38	75	30	81	138	80	159
reast milk + small suppl	5	26	5	29	8	13	3	8	16	9.4	18
reast milk + large suppl	1	5	4	23	6	11	4	11	18	10.6	13
otal	19		17		52		37		172		19[illegible]

An attempt was made to assess the effect of oxytocin treatment by a comparison of the weight curves for the babies in the two groups In this part of the analysis, we included only babies who were fed exclusively on breast milk, *viz* 189 from the oxytocin group and 197 from the control group It appeared that 32 3 per cent (or 61 infants) of the former group had regained their birth weight on the seventh day of life as against 34 5 per cent (or 68 infants) of the control cases

The influence of oxytocin on lactation disturbances during the period of establishment was evaluated on the basis of the frequencies of engorgement and of epithelial lesions and fissures of the nipple Obviously, the frequencies of these disturbances depend on the attention paid to them by the observer and also – as far as engorgement is concerned – on subjective judgment

set up rules out the possibility that the results are merely the out come of better patient care during an experiment

SUMMARY

The literature on the clinical use of oxytocin as an adjunct in the establishment of lactation is critically reviewed Some of the reported results are open to criticism because suitable control series are missing

In a clinical experiment, a nasal spray was administered to 500 patients just before each breast feed during the period of establishment of lactation Half of the patients were given about 4 I U of oxytocin, while the other half were given a placebo The two groups were comparable Oxytocin had no definite in fluence on the milk production as assessed by the food intake of the infants during the first week of life However, it seemed as if more infants with a birth weight of less than 2,500 g were able to manage on breast milk alone when the mother was given oxy tocin spray The percentages of infants who regained their birth weight within the first week of life were the same in the two groups

The frequency of engorgement of the breast was definitely reduced *in* the mothers who were given oxytocin spray while no reduction in the frequency of epithelial lesions and nipple fissures was observed However, the latter complications are in any case relatively infrequent in the hospital as a result of *intensive pro* phylactic measures

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to a great extent be attributed to difficulties experienced in the period during which lactation is being established In view of the effect of oxytocin on milk "letdown' through the glandular ducts of the breast and the assumption that oxytocin also influences the milk secretion as such, it was hoped that suitable administration of oxytocin might remedy some of these difficulties Several optimistic reports have appeared in the literature, but a critical evaluation reveals that control series are missing in most of these publications

Our closely controlled clinical experiment with nasal application of about 4 I U of oxytocin just before each breast feed showed no conspicuous effect on the series as a whole Only in the cases in which the infant weighed less than 2,500 g at birth did the establishment of lactation seem to be promoted This is reasonable enough, since it is just such infants which may have difficulty in stimulating adequately the reflex which excites the milk letdown through the glandular ducts

The investigation showed that oxytocin in the dosage and form of application employed reduced the frequency of engorgement of the breast The mechanism causing engorgement during the first week *post partum* is not known in detail, but it appears likely that oxytocin, by promoting milk 'letdown', improves the conditions for complete emptying of the duct system Even though the investigation did not reveal any influence on the frequency of fissures and epithelial lesions, the reduction in the frequency of engorgement which was demonstrated leaves open the possibility that oxytocin may be conducive to a decrease in the frequency and severity of such lesions

That the results of oxytocin treatment in the present investigation were less conspicuous than in a number of previous studies is presumably due to the fact that a control series which fulfils all reasonable requirements was provided It may also be of importance that the experiment was performed in a maternity hospital where for several years there has been a conscious effort to improve all stages in the daily routine employed for the establishment of lactation As a result the frequency of excessive engorgement and the tendency to fissures and epithelial lesions had already been substantially reduced At any rate, the experimental

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VALUE OF BACTERIOLOGICAL EXAMINATIONS IN DIAGNOSIS OF FEMALE GENITAL TUBERCULOSIS

BY

SVEN SJÖSTEDT

The improved possibilities of effectively treating genital tuberculosis have increased the importance of diagnosing the condition before irreparable changes have developed The increasing frequency with which endometrial biopsies are performed in the investigation of sterility and menstrual disorders have probably contributed to more frequent and earlier diagnosis of genital tuberculosis As an example, it might be mentioned that Sutherland (1960) reported that 216 (60 per cent) of his 369 cases of genital tuberculosis were diagnosed in association with endometrial biopsy because of sterility Since the pathological changes in sterility are not infrequently less advanced effective chemotherapy will sometimes restore fertility An increasing number of full term pregnancies following genital tuberculosis treated with chemotherapy have been reported (Kullander 1962)

Genital tuberculosis is most frequently discovered by histological examination of endometrial biopsy specimens The diagnosis should preferably be confirmed by demonstration of tubercle bacilli If the tuberculosis is localized only to the tubes and not to the endometrium however histological examination will miss the diagnosis unless the patient is submitted to laparotomy Supplementary examination with bacteriological studies is of particular value in such cases

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Bacteriological samples from patients who had received chemotherapy and who did not fill these criteria were excluded from the investigation It might be mentioned that none of the bacteriological samples from patients not satisfying these requirements proved positive

Methods

The term bacteriological examination is to be understood here as culture on solid medium according to Löwenstein, and guinea-pig inoculation

During the period 1950–1960, about 490 such bacteriological examinations were made of material from the female genital tract. All of the specimens were cultured on Löwenstein s medium and all were tested by guinea pig inoculation

Before the samples were cultured or used for inoculation, they were usually homogenized for 20 minutes in 4 % NaOH at 37° They were cultured in 2 tubes and the result was read after 6 weeks The guinea pigs were inoculated subcutaneously in the thigh The animals were killed 6 weeks later and autopsied Animals that died earlier from some intercurrent disease were examined in the same way If either culture or inoculation proved negative a guinea pig was inoculated with material from the Lowenstein s tubes or Löwenstein s tubes were cultured from the guinea pig organs The type of bacteria human or bovine was initially judged by the appearance on the Lowenstein culture All bovine strains were verified by pathogenicity tests on rabbits

In an attempt to improve the diagnosis since 1958 duplicate determinations have been made on a total of 80 endometrial specimens Half of the specimens were homogenized and treated in the way described above The other half were ground in a mortar under sterile conditions and then inoculated without further treatment into guinea pigs and cultured in Löwenstein s tubes

Results

Of 490 specimens studied tubercle bacilli were found in 70 (14 per cent) One of the cases with a growth of tubercle bacilli was excluded for reasons given above

The purpose of the present investigation was to judge the value of bacteriological examinations in a series studied histopathologically and bacteriologically

Series

The original study covered of all samples from female genitalia which were sent to the Institute of Bacteriology in Lund between the years 1950–1960 for examination for the presence of tubercle bacilli All the cases in which the diagnosis of genital tuberculosis was verified histopathologically or bacteriologically, have been included and total 96 cases One of these cases was afterwards excluded because of insufficient clinical data Among the others, the diagnosis was confirmed histopathologically in 94 cases and in one case by bacteriological examination only All the cases were examined histopathologically and bacteriologically, as a rule repeatedly

In the analysis of the data a distinction was made between endometritis and salpingitis Every patient in whom tuberculous endometritis was shown histopathologically was assigned to the group endometritis, irrespective of any simultaneous salpingitis To the group salpingitis were assigned those cases which showed tuberculous salpingitis histopathologically and in which endometrial biopsies were negative The only case that was not verified histologically and which had a clinical diagnosis of salpingitis but no demonstrable tuberculosis in the endometrium was assigned to the group salpingitis

Since chemotherapy (Para amino salicylic acid (PAS), Isoniazid (INH), streptomycin) was given in several cases and sometimes after only histopathological diagnosis and before the performance of bacteriological examination, the series must be divided into those treated with chemotherapy and those who were not treated in this way Patients who had never been treated with chemotherapy were assigned to the group 'no chemotherapy' Patients treated with chemotherapy and in whom histopathological examination showed tuberculosis after the bacteriological examination or at most half a year before the bacteriological examination were assigned to the group 'chemotherapy'

Table II *Results of the Bacteriological Examination of Tuberculous Salpingitis*

	Number of Samples											
	Endometrium		Menstrual Blood		Cervical Mucus		Vaginal Content		Tubal Pus		Total Number of Tests	
	+	—	+	—	+	—	+	—	+	—	+	—
Before chemotherapy	1	12	2	4	1	3	0	3	8	6	12	28
After chemotherapy	0	9	1	10	0	1	2	0	4	1	7	21

* 1 case clinical salpingitis was not verified histologically

in only 1 (5 per cent) of 21 cases The prospect of demonstrating tubercle bacilli in the tubal contents in tuberculous salpingitis are much greater Of 14 women, who had not received chemotherapy, tubercle bacilli could be demonstrated in 8 and in 4 of 5 who had received chemotherapy (total 63 per cent) That tubercle bacilli can be demonstrated in specimens from the endometrium cervical mucosa or menstrual blood, even when histological examination is negative implies that the bacteriological examination is a useful adjunct in the establishment of the diagnosis of tuberculous salpingitis

The results given in Tables I and II hold for combined examination by guinea pig inoculation and Löwenstein culture The two methods are compared in Table III

Table III *Comparison between Guinea pig Test and Culture*

	Human Tuberculous	Bovine Tuberculosis
Guinea-pig test positive culture positive	37	5
Guinea pig test positive culture negative	7	8
Guinea pig test negative culture positive	12	0
Total number of tests	56	13

In tuberculosis caused by tubercle bacilli of the human type both culture and guinea pig test were positive in almost two

Of the 95 cases, the diagnosis of tuberculosis was verified bacteriologically in 58 (61 per cent) In the 63 cases that had not received chemotherapy before the first bacteriological examination, tubercle bacilli were demonstrated in 50 (79 per cent) Of the 40 cases with endometritis that had not been treated by chemotherapy before the bacteriological examination, tubercle bacilli were demonstrated in 38 (95 per cent) at 1 or 2 bacteriological examinations

The results of the bacteriological examination of samples from women with tuberculous endometritis are given in Table I

Table I *Results of the Bacteriological Examination of Tuberculous Endometritis*

	Number of Samples									
	Endometrium		Menstrual Blood		Cervical Mucus		Vaginal Content		Total Number of Tests	
	+	—	+	—	+	—	+	—	+	—
Before chemotherapy	37	8	5	1	0	0	0	1	42	10
After chemotherapy	5	38	1	10	1	4	0	1	7	53

Most of the samples consisted of endometrial tissue or menstrual blood Tubercle bacilli could be demonstrated in 42 of the 51 samples (82 per cent) of the uterine mucosa or menstrual blood of the patients who had not received chemotherapy As a rule, tubercle bacilli could be demonstrated in the first specimen from the patient Only in 6 cases were repeated examinations necessary to demonstrate tuberculosis Tubercle bacilli could be demonstrated in only 7 (12 per cent) of the 59 patients, who had received chemotherapy before the bacteriological examination

The chances of demonstrating tubercle bacilli in the uterine mucosa, menstrual blood or cervical mucosa are much lower in tuberculous salpingitis (Table II)

Among patients who had not received chemotherapy before the bacteriological examination, tubercle bacilli could be demonstrated in 4 (18 per cent) of 23 samples After the patient had received chemotherapy, tubercle bacilli were demonstrated

Table V *Comparison of the Technical Results Obtained with Homogenized and Non homogenized Samples*

	No. of Samples	Living Guinea-pigs	Spontaneous Deaths of Guinea-pigs	Secondary Infection of Cultures
Homogenized samples	80	78	2	2
Non homogenized samples	80	78	2	40

Discussion

Studies for demonstration of tubercle bacilli in genital tuberculosis have given varying results Aburel *et al* (1958) showed tubercle bacilli in 64 per cent and Aldea *et al* (1958) in 71 per cent Sutherland (1960) reported a positive bacteriological diagnosis in 64 per cent of the samples, while Bedrine and Houlne (1952) found tubercle bacilli in 82 per cent Halbrecht (1958) who used culture only reported positive findings in a total of 89 per cent and Jedberg (1950) who examined operative specimens reported positive findings on bacteriological examination in a total of 94 per cent In the present series the tubercle bacilli were demonstrated in 61 per cent This figure may appear low and is due to the fact that some of the patients had received chemotherapy before the bacteriological examination In those cases of genital tuberculosis that received no chemotherapy before the bacteriological examination tubercle bacilli could be demonstrated in 82 per cent of the samples which corresponds to 79 per cent of all cases A comparison of this kind between different examiners is therefore of less value The varying results may be ascribed mainly to differences in the composition of the series of patients differences in the specimens examined and the varying number of specimens studied per patient The influence of chemotherapy is not so apparent from the literature but it is obvious from Tables I and II

Knowledge of the frequency with which tubercle bacilli can be isolated in tuberculous endometritis and salpingitis would be of greater practical value This question has however received

thirds of the specimens The guinea-pig test was positive in 79 per cent, while culture was positive in 87 per cent Both methods were positive in 40 per cent of the cases caused by the bovine type of the tubercle bacilli The guinea-pig tests were regularly positive as against only 40 per cent of the cultures In the investigation of the human type of tubercle bacilli then, culture is more reliable than the guinea-pig test, while in bovine type of tubercle bacilli the guinea-pig test is superior

Duplicate determinations were made in 80 cases Half of each sample was not homogenized The methods are compared in Table IV

Table IV *Results of the Bacteriological Examination of Homogenized and Non homogenized Samples*

	No of Samples	Positive Guinea pig Tests	Positive Cultures
Homogenized samples	80	9	10
Non homogenized samples	80	13	6

Culture gave more abundant growth of the non homogenized samples in 3 cases and equally abundant in 3 cases

Table IV shows that the guinea-pig test is more often positive if the inoculate is not homogenized The test was positive 20-25 per cent more often when the endometrious specimens were not homogenized than when they were Culture, however, gave a higher frequency of positive results when the material was homogenized This was mainly because the non-homogenized samples often caused secondary infection in the Lowenstein tube (see Table V) It should, however, be observed that in half of the samples of non homogenized material that gave positive culture, the number of colonies was greater than in the corresponding homogenized samples The series was, however, small It is clear from Table V that it involves no risk for the guinea pig to be inoculated with non-homogenized samples from endometrium The number of guinea-pigs that died spontaneously was the same among those inoculated with homogenized as among those inoculated with non homogenized material

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The high frequency of bovine tuberculosis, 12 (21 per cent) of 58 bacteriologically verified cases in the present series, is striking A few attempts have been made to ascertain how frequently genital tuberculosis is of bovine type Sutherland (1960) found only human strains when typing 147 cases of tubercle bacilli of genital tuberculosis during a 20 year period This is remarkable since Savage (1933) reported that 6 per cent of fatal cases of tuberculosis in England were due to bovine tuberculosis In a series collected from a large area of Sweden Jedberg (1950) found a frequency of 6 7 per cent bovine tubercle bacilli in genital tuberculosis The cases in the present investigation came mainly from Scania in the southern most part of Sweden In this area, Lindau (1941) found bovine strains in 8 9 per cent of the positive tests Of 1,396 cases of pulmonary tuberculosis in Scania with positive culture or guinea pig test, he found 3 3 per cent to be of bovine type Since then the occurrence of bovine tuberculosis has decreased further (Lindau, 1958) The high frequency of bovine tuberculosis in the present series suggests that the infection had started many years ago when the frequency of bovine tuberculosis was higher This also agrees with Jedbergs (1950) opinion that genital tuberculosis develops within 1 year of the initial manifestation and that most cases produce no symptoms for several years

A question of practical technical significance is whether the guinea pig test or culture gives the best results Kirchhoff (1953) and De la Pena Regidor (1960) claim that inoculation of guinea pigs is superior Kroger and Kräubig (1959) reported positive guinea pig test in 84 per cent but simultaneous growth on culture in only 53 per cent Of examinations carried out on sputum it might be mentioned that Saxholm (1958) who studied NaOH homogenized material found the guinea pig test superior In the present series culture gave positive results in 87 per cent and guinea pig inoculation in 79 per cent Only Halbrecht (1958) found positive culture to be equally common but it should be observed that he cultured material from each patient on anything up to 10 occasions

In contrast to what was found by most previous investigators, in the present series culture proved at least equally good or

little attention in the literature Bedrine and Houlne (1952) claim that tubercle bacilli can always be demonstrated in endometritis Aldea *et al* (1958) believe, however, to have dis proved this by having found tubercle bacilli histologically in only 65 per cent In the present series tubercle bacilli could be de monstrated in 82 per cent of the samples from 40 women who had not received chemotherapy (Table I) In these women, studied bacteriologically on one or two occasions, it was possible to demonstrate tuberculosis in 38 (95 per cent) In untreated tuberculous endometritis, then, it should be practically always possible to demonstrate tubercle bacilli

The frequency with which tubercle bacilli can be demonstrated in patients with tuberculous salpingitis alone is not given in definite figures in the literature In compilations a group is often given with positive bacteriological findings in the endometrium or menstrual blood and negative histopathological findings in the endometrium This group can very probably be regarded as tuberculous salpingitis Negative histopathological in association with positive bacteriological findings were thus found by Aldea *et al* (1958) in 25 per cent of his series, by Halbrecht (1958) in 35 per cent, by Berencsi *et al* (1958) in 11 per cent, and by Suranyi *et al* (1958) in 19 per cent In the present series the corresponding figure was 18 per cent The variations are due to some extent to differences in the composition of the series An important factor is probably how thoroughly the examinations are made Halbrecht (1958) thus repeated his examinations until 1 or 2 positive or 10 negative cultures were obtained It is obvious, however, that the bacteriological examination is of con siderable value, because it enables a diagnosis of genital tuber-culosis to be made in a fair number of cases in which laparotomy or peritoneoscopy would otherwise have been necessary for a firm diagnosis

In the literature it has been discussed whether endometrium or menstrual blood is better for demonstrating tubercle bacilli (Aldea *et al*, 1958, Kroger and Kräubig 1959) The question is still open and the present series with its small number of samples of menstrual blood cannot contribute to the solution of this problem

In tuberculous endometritis not treated with chemotherapy one or two bacteriological examinations of the endometrium or menstrual blood resulted in demonstration of tubercle bacilli in 95 per cent. In tuberculous salpingitis that had not been treated with chemotherapy, tubercle bacilli could be demonstrated in 18 per cent of samples from the endometrium, menstrual blood and cervical mucosa and in 63 per cent of samples of the tubal content The possibility of demonstrating tubercle bacilli was much smaller after chemotherapy

In the bacteriologically verified series, 21 per cent of the cases were caused by tubercle bacilli of bovine type and 79 per cent of human type

Culture on Lowenstein s medium (87 per cent positive) was equally effective or superior to guinea pig inoculation (79 per cent positive) in the diagnosis of infections due to tubercle bacilli of human type while guinea pig inoculation was superior in the diagnosis of bovine type

Inoculation of guinea pigs with non homogenized endometrium was superior to inoculation with homogenized material and involves no disadvantages On culture of untreated endometrium, on the other hand, 50 per cent of the specimens were secondarily infected

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superior to the guinea pig test in the diagnosis of tuberculosis of human type. In tuberculosis of bovine type on the other hand, the guinea-pig test was superior.

The possibility of improving the bacteriological examination by treating the material to be examined less with chemicals, has received little attention in the literature. Aburel *et al* (1958) add penicillin to the menstrual blood and inoculate it directly on Lowenstein's medium. Kroger and Kräubig (1959) add chloromycetin to menstrual blood and then inject it directly into the guinea-pig. The authors say nothing about the advantages or disadvantages of the methods. Saxholm (1958), on the other hand, states that inoculation of guinea-pigs with untreated sputum gives markedly better results than homogenized material. This was confirmed in the present series. On culture of material from women with untreated endometritis guinea pig inoculation was positive in all 12 cases with non-homogenized material, as against only 9 when the material had been homogenized.

A prerequisite for inoculation of non homogenized material is that the mortality among the guinea-pigs is not too high. Saxholm (1958) found on inoculation of sputum that the mortality with homogenized material was 4.2 per cent and with non homogenized 5.8 per cent. In the present series the mortality was 2.5 per cent for both homogenized and non-homogenized material.

In the present study the frequency of secondary infection on culture was considerable and so high as to raise the question as to whether it is worth while culturing non-homogenized material. Since the number of colonies was possibly greater on culture of non-homogenized material, it would perhaps be an advantage if such material could be used. Addition of antibiotics to untreated samples might perhaps reduce the frequency of secondary infection sufficiently to make culture practicable.

SUMMARY

Ninety five cases of genital tuberculosis were studied histopathologically and bacteriologically with guinea pig inoculation and culture on solid Lowenstein's medium.

In 94 cases the diagnosis was established histopathologically

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URETERIC INJURY FOLLOWING TOTAL HYSTERECTOMY

BY

THOR DAHLE SIRI TOVERUD AND KJELL TRÆTTEBERG

Occasionally gynæcological surgery is complicated by unilateral or bilateral ureteric injury, and in most cases the operation in question is hysterectomy Radical hysterectomy for carcinoma of the uterus has always been and still is, attended by a great risk to the ureter Ureterovaginal fistula is the most serious complication of such an operation But even following simple hysterectomy for benign disease, injury to the ureter sometimes occurs and, as pointed out by Morrison, injuries still play a part in the morbidity and mortality of simple hysterectomy

Ureteric injury depends on many different factors, but mainly on the nature of the case operated upon and the skill of the gynæcologist Most often the damage to the ureter is confined to the terminal part where the ureter crosses the uterine vessels Here, during the hysterectomy, bleeding is often seen and the vessels are ligated Most ureteric injuries occur in an attempt to control this hæmorrhage The injury may be inflicted by clamping, cutting or ligating the ureter, or it may be indirectly caused by disturbing the blood supply or the normal anatomical position of the ureter, or by bringing about fibrosis in the ureteric wall or the periureteric tissue The pathology may be of varying degree and, consequently the clinical picture may range between the most dramatic and the most silent one

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Fig 1b



Fig 1 a

Fig 1 K.B 42 years old total hysterectomy and bilateral salpingo-oophorectomy for myoma of the uterus *a)* pre-operative urogram showing moderate bilateral hydroureter *b)* post-operative urogram (4 5 months) with normal appearance in upper urinary tract

stricture of the terminal ureter (0 5 per cent) This incidence is remarkably low considering that a number of patients underwent radical hysterectomy and lymph node dissection for squamous cell carcinoma of the cervix

Most papers dealing with the subject do not differentiate between ureteric injury following hysterectomy for a benign and for a malignant disease It must be obvious that ureteric obstruction following surgery for carcinoma of the cervix may be due to the malignant spread of the tumour and not to the surgery, which is not the case after operations upon patients with a benign disease In studying the possible damage to the ureter following hysterectomy, only patients without malignant disease should be considered Morrison in 1960 reported an investigation into the state of the urinary tract in 100 patients before and after the operation of simple hysterectomy, with particular reference to the ureter In the main the operation was performed for benign conditions but nine patients had a carcinoma of the body of the uterus, and two patients had a carcinoma of the ovary Morrison s excellent results showed no gross injury to the ureter, and in only three patients did hysterectomy produce a temporary dilatation, which disappeared within 18 months However it may be mentioned that in a number of the cases reported by Morrison, a subtotal and not a total hysterectomy was performed

The present study was undertaken to assess the possible danger to the ureter with special regard to silent injuries, of total hysterectomy for benign conditions Consequently, every patient in whom the uterus had to be removed underwent a total hysterectomy To avoid any selection of the patients no subtotal hysterectomy was performed in the period of study (August 1st, 1957, to December 31st 1958) This may be criticised but it seemed necessary to eliminate as many variable factors as possible which might influence the value of the results

Material

During one and a half years a total of 118 patients mainly suffering from uterine fibroids, underwent total hysterectomy and in addition in 21 cases unilateral and in 23 cases bilateral

The diagnosis of gross injury to the ureter with resultant ureteric fistula or anuria is never difficult because the symptoms cannot be overlooked However, not all ureteric injuries are gross and attended by such alarming symptoms Some of them give rise to lumbar pain, which may be overlooked, and others give no symptoms at all

While the diagnosis and treatment of gross ureteric injury is often mentioned in the literature, until recently little attention had been paid to silent injury Eddy and Miller in 1937 tried to find out how often the latter occurs, by using routine cystoscopic examinations in the follow-up of patients after hysterectomies, and their conclusion was "that ureteral or bladder injuries are not necessarily a frequent complication of total hysterectomy" Incidentally, only in four cases did they use urography for the purpose of detecting a possible silent injury to the ureter From autopsies, however, we know that silent injury to the ureter following hysterectomy may cause serious, but clinically undetected, anatomical and functional disturbances Unilateral ligation of the ureter, kinking of the ureter or production of fibrosis in the ureteric wall and the periureteric tissue in the post operative period, may give only slight symptoms or none at all, and yet later on this injury may give rise to hydroureter, hydronephrosis and a complete cessation of renal function In 1939, Quittman Newell gave a detailed report of 15 patients with injured ureters following gynæcological operations In six cases the patients died in the early post-operative period and in five of these cases he found at autopsy that one ureter had been ligated, three on the right and two on the left side Two of the patients had had a complete abdominal hysterectomy performed for carcinoma of the body of the uterus, and three had had the same operation for myoma of the uterus

At the present time it is not possible to assess the frequency of silent ureteric injury following hysterectomy without pre- and post-operative urographic studies In 1954 Conger, Beecham and Horrax reported an analysis of such studies on 200 patients undergoing major gynæcological surgery The incidence of clinically unrecognized ureteric injury was low, they only found one case with complete ureteric obstruction due to impassable



Fig 2b



Fig 2 a

Fig 2 O H, 50 years old total hysterectomy and bilateral salpingo-oophorectomy for myoma of the uterus *a)* pre-operative urogram showing considerable dilatation of right ureter *b)* post-operative urogram (4 months) showing no dilatation of right ureter

discharge indicated a urinary fistula, and by vaginal inspection leakage of urine from a necrotic area at the vault of the vagina was seen Urography on the 33rd day after the operation showed a dilatation of the right ureter and contrast medium in the vagina On cystoscopic examination the ureteric openings in the bladder had a normal appearance and urine came intermittently from the left orifice No efflux of urine was seen from the right orifice The left ureter was catheterized without difficulty, but on the right side the catheter stopped 1 5 cm from the ureteric orifice

No attempt was made to pass the ureteric catheter beyond this obstruction and within a week the urinary leakage discontinued The patient left hospital on the 44th day after the operation At follow up examinations the patient was free from symptoms, and 4 5 months post operatively urography showed a normal appearance of the ureters on both sides

The patient with the silent injury to the ureter was 68 years old and had a total hysterectomy and bilateral salpingo-oophorectomy performed because of post menopausal bleeding The post operative course was complicated only by wound infection and the patient was discharged the sixteenth day after the operation At pre operative urography the urinary tract seemed normal At post-operative urography five months after the operation a ureteric stricture on the left side was seen about 4 cm from the vesical orifice and there was dilatation of the ureter above this point At urographic re examination 2 5 years after the operation no deterioration was seen No treatment was advised especially since the obstruction was partial and unilateral and the patient was 68 years old and was overweight

In a third patient, aged 46, a urinary fistula in the vagina was diagnosed on the fourth post-operative day but this fistula was assumed to be vesico- and not uretero vaginal The post-operative course was also complicated by pulmonary embolism The urinary fistula closed spontaneously, and the patient was discharged on the 47 th day after the operation Urography performed six months post-operatively showed no abnormality in the upper urinary tract

salpingo-oophorectomy was performed One hundred and fourteen patients had pre-operative urography performed, and, for the purpose of detecting possible silent injuries following hysterectomy, urography was also performed four to six months after the operation Unfortunately, 16 patients refused radiological re examination, this leaves a series here presented of 98 patients who underwent a total hysterectomy and had pre- and post-operative urography performed There was no operative death

Results

Dilatation of the ureter was seen in both pre- and post-operative urographic examinations in a number of cases

In the *pre-operative* urographic examinations dilatation of one or both ureters was seen in 18 patients or 19 8 per cent In 15 cases the abnormality was bilateral and in 3 cases it was unilateral The dilatation was due to pressure from the pelvic tumour, and, as is frequently seen in pregnancy, was most marked on the right side All the cases with unilateral dilatation involved the right side The dilatation was of varying degree, in two cases it was considerable, in the other cases it was moderate or slight

In eight patients displacement of the pelvic ureter was observed, but in a number of cases the terminal part of the ureter was not visualized

In the *post-operative* urographic examinations, made four to six months after the operation, the pre-operative dilatation present in the 18 patients detailed above, had disappeared in 14, in the remaining four patients the dilatation was still present, but the condition was considerably improved

In the 98 patients examined there were two surgical injuries to the ureter In one case a gross injury with ureterovaginal fistula occurred, in the other case a silent injury

The patient with the gross injury was 46 years old, she was unmarried and had never been pregnant She underwent a total hysterectomy and bilateral salpingo-oophorectomy for fibroids in the uterus, which was the size of a fœtal head at term Pre operative urography showed moderate bilateral dilatation of the ureters On the eighth day after operation a profuse watery vaginal



Fig 3b



Fig 3 a

Fig 3 B F 46 years old total hysterectomy and bilateral salpingo-oophorectomy for myoma of the uterus Ureterovaginal fistula which closed spontaneously *a)* pre-operative urogram showing moderate dilatation of right ureter *b)* post-operative urogram (4 months) showing normal appearance of upper urinary tract

diagnostic deafness or to silent pathology It is likely that if urography was used more frequently and earlier in the post-operative period following total hysterectomy, more transient silent injuries would be seen By performing urography in the third post-operative week Morrison found that simple hysterectomy produced a temporary dilatation of the ureter in three out of 80 patients, and that the dilatation disappeared within 18 months

In the 98 patients examined, post-operative urography four to six months after the operation showed a dilatation of the ureter in five cases In four of these the dilatation was already visible in the pre-operative urograms, but had considerably decreased by the time of the second urography The possibility can not be ignored that this dilatation may be due to the operation performed but it seems more likely that it is due to the back pressure changes which were seen pre-operatively In only one case was the dilatation certainly due to surgical injury to the ureter In the remaining 93 patients no abnormality in the upper urinary tract was seen

One of the authors (Dahle) has in a previous paper shown the danger to the ureter following combined radiologic surgical treatment of carcinoma of the cervix In 96 stage I patients four ureteric fistulæ occurred, and by post operative urography abnormality of the upper urinary tract was seen in 22 cases This is in accord with the incidence of abnormalities in the upper urinary tract found by Meigs and Liu Douglas and Birnbaum and others In the series here presented only two ureteric injuries were seen following simple hysterectomy for benign conditions which makes a contrast to the incidence of ureteric injuries following radical hysterectomy

SUMMARY

In 98 patients who underwent total hysterectomy for benign conditions pre operative and post operative urography was performed the latter four to six months after the operation Pre operatively dilatation of the ureter on one or both sides was seen in 18 patients, due to the tumour present At post operative urography the dilatation of the ureter had disappeared in 14 pa



Fig 4 A M, 68 years old, total hysterectomy and bilateral salpingo-oophorectomy for post menopausal bleeding Post operative urogram (5 months) showing dilatation of left ureter (silent injury)

Discussion

There is no doubt that a silent injury to the ureter may be overlooked, but one may speculate, as Conger, Beecham and Horax do, "as to whether the overlooked cases exist due to

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TEN YEAR END RESULTS, RADIOLOGICAL TREATMENT OF CARCINOMA OF THE CERVIX

BY

H L KOTTMEIER

The five year cure rate has been generally accepted for estimating the results of treatment in cancer of the cervix although this does not mean absolute freedom from recurrence five years after initial therapy The Editorial Committee for the Annual Report is perfectly aware of this and has requested a survey of the results after periods of seven and ten years *Table I* presents the results ten years after initial treatment at 12 institutions, each of which report on at least 50 Stage I cases treated between 1944 and 1948 and which contain no cases treated primarily by surgery It is evident that out of 3 676 cases in all stages considered as symptom free at five years 354 or 9 6 per cent died from recurrent cervical carcinoma within the following period of five years while in 301 cases the patients died from intercurrent disease Although these figures are of interest we doubt whether they permit the drawing of any reliable conclusions as experience shows that many institutions have considerable difficulty in obtaining information concerning patients treated more than five years previously

A prerequisite for estimating therapeutic results in carcinoma of the cervix by any kind of therapy is the primary division of cases into four clinical stages An unselected series of 1,891 cases of carcinoma of the cervix treated by irradiation at the Radiumhemmet in the years 1944 to 1949 inclusive will be presented and

tients, and in four the condition was considerably improved In one case post-operative urography showed unsuspected surgical injury to the ureter In the remaining 93 patients no abnormality in the urinary tract was seen One patient had a gross injury to the ureter She had a ureterovaginal fistula which closed spontaneously and did not leave any abnormality in the upper urinary tract at urography

The risk of ureteric injury following total hysterectomy for benign conditions is relatively low as compared with the risk following radical hysterectomy for malignant diseases

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Eight hundred and thirty-eight of the 1,891 patients initially treated by irradiation in the years 1944 to 1949 are living without evidence of recurrence of carcinoma of the cervix at five years, i e an apparent recovery rate of 44 3 per cent (*Table III*) Seven hundred and one patients are symptom free at ten years, i e a ten year apparent recovery rate of 37 1 per cent

Table III *Carcinoma of the Cervix Patients Treated in 1944 to 1949 Five year and Ten year results*

Stage	Number of Cases Treated	Living at 5 Years without Evidence of Carcinoma of the Cervix		Living at 10 Years without Evidence of Carcinoma of the Cervix	
		No of cases	Per cent	No of Cases	Per cent
I	289	220	76 1	200	69 2
II	957	476	49 7	386	40 3
III	491	134	27 3	109	22 2
IV	154	8	5 2	6	3 9
Total	1 891	838	44 3	701	37 1

Table IV *Carcinoma of the Cervix Patients Treated in 1944 to 1949*

Stage	Living at 5 Years without Evidence of Carcinoma of the Cervix	Patients Died within a Period of > 5 Years to 10 Years from: Cancer of the Cervix		Intercurrent Disease Including other Malignant Tumours (figures in brackets)		Living at 10 Years without Evidence of Cancer of the Cervix	
		No of cases	Per cent	No of cases	Per cent	No of cases	Per cent
I	220	8	3 6	12 (2)	5 5	200	90 9
II	476	42	8 8	48 (18)	10 1	386	81 1
III	134	13	9 7	12 (4)	9 0	109	81 3
IV	8	2		–		6	
Total	838	65	7 8	72 (24)	8 6	701	83 7

A recurrence of the carcinoma of the cervix was diagnosed in 65 of the 838 cases clinically considered as symptom free at five years i e in 7 8 per cent of the cases The figures in the stages

Table I *Carcinoma of the Cervix Results of Treatment at 12 Institutions Each of Which Reports on at Least 50 Stage I Cases Treated between 1944 and 1948 and Whose Series of Cases Contain no Cases Treated Primarily by Surgery*

	No of Patients Treated 1944–48	Alive with no Evidence of the Disease after a Period of						Dead from Intercurrent D during a Period of			
		5 years		7 years		10 years		5 years		7 years	
		No	%	No	%	No	%	No	%	No	%
Stage I	1,704	1,183	69 4	1,106	64 9	1 028	60 3				
Stage II	3,430	1,707	49 8	1,556	45 4	1,397	40 7				
Stage III	2,552	709	28 1	623	24 7	546	21 6				
Stage IV	692	77	11 1	59	8 5	50	7 2				
Total Stages I–IV	8,348	3,676	44 0	3,344	40 1	3,021	36 2	267	3 2	405	4 9

discussed in detail All cases have been traced Combined intra cavitary radium and external roentgen therapy, in accordance with the classical Stockholm method, was given A number of cases, treated in 1949, however, were given a more individualized scheme of irradiation, and this gave better results than those ob tained in previous years *Table II* gives the five-year apparent recovery rate in all patients examined at the Radiumhemmet in the years 1949 to 1953 inclusive

Table II *Carcinoma of the Uterine Cervix Five-year Apparent Recovery Rates for the Years 1949 to 1953*

Stage	No of Cases and Per cent of all Stages	Five year Relative Apparent Recovery Rates No of Cases Per cent	Dead from Inter current Disease No of Cases
I	291 = 15 7 %	256 = 88 0 %	7
II A	510 = 27 6 %	352 = 69 0 %	27
II B	519 = 28 1 %	244 = 47 0 %	16
III	391 = 21 1 %	134 = 34 3 %	4
IV	139 = 7 5 %	9 = 6 5 %	2
I–IV	1,850 = 100 0 %	995 = 53 8 %	56
	16 not accepted for treatment		
	1,866	995 = 53 3 % absolute cure rate at 5 years	

from 65 to 54 cases or from 7 8 to 6.4 per cent The corresponding figure for Stage I would have been 2 7 per cent for Stage II, 7 3 and for Stage III, 8 9 per cent.

Previously I pointed out that 24 patients had evidently died from a malignant tumour other than the carcinoma of the cervix. The neoplasm was situated in the ovaries in one case, in the urinary bladder in another and in the rectum in three cases If the 11 cases described above and allotted to the group of recurrent carcinoma of the cervix had been considered as intercurrent deaths, the number of patients dying from a new primary growth in the pelvis would have amounted to 8 cases I do not think that this observation supports the opinion that irradiation predisposes to carcinoma

The appearence of multiple primary malignant tumours is of great interest Several authors have expressed the view that it is possible that in these conditions one has to deal with a kind of constitutional disability, an inherent predisposition to carcinoma Although we have seen multiple neoplasms in nearly 6 per cent of our cases of carcinoma of the cervix – in one case, eight different malignant tumours – we do not feel qualified to draw any conclusion as far the biological fact hypothesis is concerned.

A comparison of statistics on therapeutic results requires among other things details of the criteria for reporting a case as an inter current death. The principle at the Radiumhemmet is to consider cases as intercurrent deaths only if *post mortem* examination was carried out or if careful examination performed within a few weeks prior to the death of the patient revealed no sign of malignancy Among the 838 living patients symptom free at 5 years 48 patients were considered to have died from intercurrent disease in the course of the following five years The 24 patients described above who died from another primary neoplasm, are not included in these 48 cases Although our criteria for allotting a case as an intercurrent death are strong we cannot exclude that the patient had residual cancer A direct comparison of therapeutic statistics is therefore impossible To illustrate this fact, not less than 10 out of the 65 patients referred as dead from recurrent carcinoma of the cervix in my report actually died from acute pneumonia myocarditis cerebral hæmorrhage or nephrosclerosis None of the

Table V *Carcinoma of the Cervix Patients Considered Symptom-free 5 Years with Recurrence at 5 to 10 Years after Initial Treatment*

Stage	Number of Cases with Recurrence		Recurrence in the Pelvis Except the Pelvic Wall		Recurrence in the Pelvic Wall		Recurrence in Distant Organs	
I	8		1		2		5	
II A	25	42	6	13	11	15	8	14
II B	17		7		4		6	
III	13		4		2		7	
IV	2		1		–		1	
Total	65		19		19		27	

were 3 6 per cent for Stage I, 8 8 per cent for Stage II, and 9 per cent for Stage III The corresponding figures for intercurren deaths were 5 5 per cent for Stage I, 10 1 per cent for Stage II and 9 0 per cent for Stage III

Twenty-four of the 72 patients classified as intercurrent deaths succumbed from a malignant growth which histologically proved not to be secondary to the primary neoplasm in the cervix. In our opinion it is, as a rule, impossible to distinguish a new primary growth from a recurrent or metastatic neoplasm if microscopical examination has not been performed As a matter of fact, 11 out of the 65 cases recorded as dead from recurrent carcinoma of the cervix actually presented clinical signs of another primary carcinoma but as no microscopical examination was performed, the cases were classified as recurrent carcinoma of the cervix The growth was apparantly a carcinoma of the lung in 5 out of the 11 cases, while in 3 other instances a tumour in the brain, in the liver or in the pancreas was presumed Finally the growth was situated in the vagina in two cases, and in the endometrium in one case Histological examination was performed in the three cases last mentioned The pathologist considered the neoplasm most likely to be a primary carcinoma in the vagina and in the corpus, but as he was unable to exclude definitely the possibility of a recurrence from the primary lesion in the cervix these three cases were also allotted to the series of cases with recurrent carcinoma If the 11 cases described had been recorded as intercurrent deaths, the number of recurrent cancers would have apparantly decreased

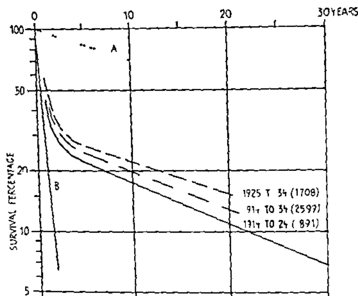


Fig 1 Carcinoma of the cervix Survival rate in per cent 30 to 10 years following initial radiotherapy at Radiumhemmet in 1914 to 1934 incl a) Life expectancy curve for Swedish women 60 years of age b) Survival rate in per cent for untreated patients in regard to time of diagnosis of carcinoma

the recurrence was in the uterus, in the vagina, or in the para metrial tissue, while in a further 19 cases it appeared in pelvic lymph nodes and in 27, in distant organs Six hundred ninety six of the 838 cases living symptom free five years after initial therapy were allotted to the operable Stages I and II In 14 of the 696 cases, the recurrence appeared in the pelvis, *i e* in 2 per cent of the cases In these 14 cases are included 3 cases in which it is likely that the recurrent carcinoma in the corpus or in the vagina was in fact a new primary neoplasm

Finally, with the intension of presenting a complete report, three cases will be described which are living at present without any evidence of cancer In one case of Stage III a recurrent carcinoma appeared in the cervix eight years after initial irradia tion The patient was treated by electro-fulguration In two cases of Stage I, a primary carcinoma of the endometrium was diagnosed

patients had clinical signs of recurrent or metastatic carcinoma. *Post-mortem* examination revealed in 3 cases an isolated mass in the liver or close to the bile duct, the size of a pea or a cherry, while in another case a metastatic tumour the size of a hazelnut was found in the right adrenal. Microscopical examination of pieces taken from bronchopneumonic areas in the lungs revealed circumscribed small foci of malignant cells in three cases. X-Ray examination of the lungs had not demonstrated any metastatic lesion. Finally, circumscribed small foci of epidermoid carcinoma were seen in the heart and mediastinum of one case, and in the cortex of the brain of another. No residual carcinoma was demonstrated in the pelvis except in the last of the 10 cases, in which a small metastatic growth was found in the right ovary. As mentioned previously, these 10 cases were allotted to the group of cases with recurrent cancer of the cervix. If no *post mortem* examination had been carried out there is no doubt that these cases would have been considered dead from intercurrent disease. Actually it is questionable whether it is not more appropriate to consider these 10 patients as intercurrent deaths as they did not show any clinical symptoms of residual carcinoma.

We have evidence of invasive carcinoma remaining silent for years. As an example a patient, 68 years of age, was operated upon for a carcinoma of the uterus. A lymph-node metastasis the size of a plum fixed to the left part of the sacrum could not be removed. Rœntgen therapy was given in moderate doses. The patient was killed in a street accident eight and a half years following the hysterectomy. *Post mortem* examination showed a lymph-node the size of a plum on the left side of the sacral promontory. The lymph-node was completely destroyed by the carcinoma. A capsule a few mm. thick surrounded the growth.

It is evident from this discussion that only 44 instead of 65 of the 838 patients could have been considered dead from recurrent carcinoma of the cervix *from five to ten years following* initial irradiation. The percentage figure would then be 5.3 instead of 7.8 per cent. The corresponding figures for the stages would be for Stage I, 2.7 per cent, for Stage II, 5.4, and for Stage III, 8.2 per cent.

In 19 of the 65 patients with recurrent carcinoma of the cervix

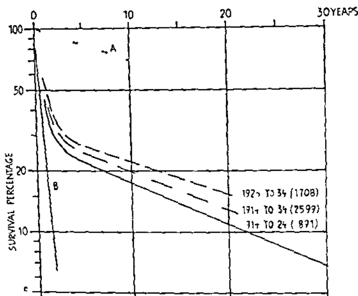


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seven and nine years respectively after the treatment of the cervical carcinoma A panhysterectomy was carried out If these 2 cases are included among the 14 cases of Stage I and II with recurrent carcinoma in the pelvis mentioned above, the total number of cases with a recurrent or with a new primary growth in the pelvis amounts to 16 cases, *i e* to 2 3 per cent of the 696 cases in Stage I and II considered as symptom-free at five years

Conclusion

A report has been given of ten year end results in a series of 1,891 cases of carcinoma of the cervix treated by irradiation at the Radiumhemmet in the years 1944 to 1949 I have tried to call attention to several facts which have to be considered in estimating statistics on therapeutic results Recurrences of carcinoma of the cervix can become evident even after five years have passed since initial therapy A positive recurrence causing clinical symptoms occurred in 5 3 per cent of the cases which were considered *free from cancer at the end of five years* A recurrence may occur ten years or more after initial therapy Fig 1 presents the ten to thirty-year survival rate in 2,599 cases of carcinoma of the cervix treated by irradiation in the years 1914 to 1934 inclusive The cases are divided into two groups as only intracavitary radium was given to the cases treated prior to 1925 The observation is of interest in that the curve for survival rate in patients living symptom free at ten years after initial irradiation is almost identical to the life expectancy curve for Swedish people aged 60 years This implies that 35 per cent of patients treated for carcinoma of the cervix by irradiation in the years 1914 to 1934 would have been cured for ever from the cervical cancer This observation can be set in comparison to the survival rate in 262 patients who were suffering from carcinoma of the cervix and did not receive any kind of therapy All patients were dead from the cancer within two years of the diagnosis being made Only 3 patients were living five years after the date of the first symptoms

SUMMARY

A detailed investigation with regard to ten year results in 1,891 cases of carcinoma of the cervix treated by primary radio therapy is presented The author emphasizes the various facts which should be considered when estimating the presentation of therapeutic results

A recurrence causing clinical symptoms occurred in 5 3 per cent of the cases that were considered free from cancer five years following initial therapy

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IN MEMORIAM

SAKARI PARVIAINEN

1909 — 1962

On February 9 1962 Professor Heikki Sakari Parviainen unexpectedly died at the age of 52 years We his friends and colleagues still find it hard to realize that we have lost him thus in the prime of his life His characteristic energy and zest were thoroughly in evidence as late as last autumn at the committee meetings of the Vienna Congress of Gynæcology

Sakari Parviainen was born at Joensuu in 1909 and graduated as a licentiate at Helsinki University in 1936 His thesis for the doctorate which he publicly defended in 1941 dealt with methods of improving the prognosis of premature children The

the most recent literature on his subject, and his lectures were always up to date Large numbers of Finnish doctors recall him as a thorough, sympathetic teacher, who was ever ready to share the fruits of his profund learning with his pupils

During his last years, Parviainen was worried about the exter nal working conditions and the lack of space and facilities in his clinic He played an extremely active and dedicated part in the planning of a new building not only in outline but also in working out the details of the blueprints He shared the fate of his prede cessors in not being allowed to see the full realization of his wishes and plans at his death, the digging of the foundation of his new clinic was still going on

As a practising doctor and clinician, Parviainen was exemplary He never thought of himself At any hour, day or night he was ready to follow his calling and to ease the pains of others To him, a patient was never a case a mere number on a journal or a sheaf of data from the laboratory He suffered with his patients and worked not only with diseases but with living human beings

In spite of a heavy load of research, teaching and clinical work, Parviainen found time for an active contribution to several pro fessional organizations He was a member of the Finnish Medical Association s committee for postgraduate training, of its Delegation, and for many years of the Board of the Finnish Society of Gynæcology, whose chairman he was in 1958–60 At meetings, including Scandinavian and international congresses, colleagues were struck by his pleasant easy manners and by his interesting papers and lectures He was frequently called to participate in various meetings working out problems related to his subject

Parviainen s home was always open to friends and students Its atmosphere bore witness to his wide cultural interests In pri vate life he followed the same high ideals as he emphasized in his teaching His analytic bent of mind was the basis of his charac teristically quiet yet delightfully keen sense of humour

By coming in the midst of his career Parviainen s death was doubly tragic Even now his achievements are great and lasting A host of pupils and acquaintances will remain mourning a cherished professor colleague and friend

Lauri Rauramo

choice of career apparently gave him no difficulties. Immediately after graduation he worked as an assistant at the Viipuri Women's Clinic under Mauno Rauramo. In 1938 he transferred to the Women's Clinic of Helsinki University Hospital, where he specialized under Seth Wichmann and held an assistantship until 1943. He was awarded specialist's rights in gynæcology and obstetrics in 1940. Like most of his colleagues in Finland he had to give a number of his best years to the Army. During the war he saw active duty as chief medical officer of an infantry regiment as well as in field and base hospitals. When the war was over he eagerly returned to research, having been appointed Docent of gynæcology and obstetrics in 1944. In the same year he became Assistant Chief of the First Women's Clinic of Helsinki University, where he remained as Mauno Rauramo's closest collaborator until 1952, when he was given a personal professorship at Helsinki. He had contested chairs at Turku in 1946 and at Helsinki in 1951, and both times the respective faculties declared him well qualified for a professorship. In 1956 he was called to the permanent chair of gynæcology and obstetrics at Turku University, whose Women's Clinic he headed until his death.

Parviainen was especially interested in questions linked with maternity welfare. Beside his main work he supervised the municipal maternity welfare centres of Helsinki for several years and taught maternity welfare at his Clinic. His research and publications also tended towards the study of the role of prophylaxis in obstetrics, and for his inaugural lecture at Turku he chose a subject close to his heart: the importance of prophylactic measures in gynæcology and obstetrics. Among the problems he investigated were the lowering of perinatal mortality especially among premature children, the early diagnosis of uterine cancer, the risk of prolonged labour, and above all toxæmia of pregnancy. More than one hundred publications testify to his industry, and they have been internationally praised as original and versatile.

Apart from research, the education and training of new generations of doctors and gynæcologists was the main focus of Parviainen's interest. His pupils remember the high ethical ideals which Parviainen himself applied to his work and whose inculcation was an essential part of his teaching. He was thoroughly at home with

In 1941 Barnes reported a case with a 29 weeks fœtus, Berry (1955) with a 16 weeks fœtus, Ruffolo (1956) with a 28 weeks fœtus, Kohl (1960) with a 20 weeks fœtus and Goddard (1960) reported three cases with varying fœtal ages

Other cases were reported by Beltz & Hutchins (1951), Acosta Sison (1954), Taylor (1957), Waters & Grunden (1943), Favreau & Belanger (1939), MacRae (1951), Cline (1946), and others

Case Report

F R. (Hospital No 1842) Admitted on 5.4 1961 to Alexandria University Hospital (Chatby)

The patient was thirty-eight years female married for 15 years She had had seven ful term normal labours the last one two years previously She claimed to have amenorrhea for four months and slight vaginal bleeding for four days before admission When first examined the pulse rate was 69 temperature 37 C B P 180/120 The urine contained albumin +++ There was marked œdema of the lower limbs and abdominal wall The uterine fundus which was felt with difficulty because of the marked œdema reached to the level of the umbilicus Identification of fœtal parts was impossible No fœtal heart sounds were audible Vaginal examination revealed a soft closed cervix through which moderate bleeding was visualised

A clinical diagno is of vesicular mole was based on the undue enlargement of the uterus and the associated signs of severe toxæmia A plain X ray and an assay of the gonadotropins in urine was intended but half an hour after the examination the patient was seized with a severe attack of bleeding and she expelled spontaneously a twenty weeks living male fœtus with a crown heal length 16 5 cm weighing 316 gm and looking normally developed The umbilical cord was attached to a discoid placenta 10 cm in diameter which showed no vesicular degeneration on naked eye examination. The expulsion of the fœtus was accompanied and followed by the expulsion of many vesicles and a big blood clot.

However the spontaneous expulsion was incomplete and digital evacuation was undertaken More vesicles were removed and during the exploration of the uterus the site of the placental attachment was felt and localised to a small area to the left on the anterior wall otherwise the surface of the uterine cavity was smooth

Apart from slight bleeding and a low grade pyrexia the patient was perfectly well on discharge A male frog test on the second day after evacuation was positive in 1/200 dilution after two weeks it was positive with undiluted urine and negative in dilution. Two months later the frog test was negative

Microscopic examination of the placenta showed no vesicular degenera

Sherif M., Acta obst. et gynec scandinav 41 208 1962

From the Department of Gynæcology and Obstetrics, Alexandria University Egypt, U A R (Prof Dr H Toppozada M CH)

A CASE OF VESICULAR MOLE WITH A TWENTY WEEKS LIVING FŒTUS

BY

M. SHERIF M. CH *

The association of a vesicular mole with a well developed fœtus is very uncommon The rarity had been emphasised by Williams (1918) and Mahfouz (1949) who considered it exceptional for any traces of fœtus or amniotic sac to be found with vesicular moles

In 9,501 deliveries during 1932–1941 at the Queen Hospital in Honolulu, Bowles (1943) reported only one instance of co existing fœtus and mole

No such association had been reported at the Chatby University Hospital, Alexandria, among 30,600 hospital deliveries and abortions including 38 cases of vesicular mole

Hertig (1947) in a pathologo-clinical review of two hundred moles reported only one case of fully established vesicular transformation of the placenta associated with a fœtus in a pregnancy of over twenty weeks duration

In 1956 Ruffolo reported a case of vesicular mole with seven months fœtus and estimated the incidence of the association to be approximately one in 105 000 pregnancies

A review of the literature showed that the association had been reported at varying fœtals ages Cases in which the child survived were reported by Bowles (1943) Mueller & Lapp (1950), Sitaratna (1960), and Goddard (1960)

* Lecturer in Gynæcology & Obstetrics

In 1941 Barnes reported a case with a 29 weeks fœtus, Berry (1955) with a 16 weeks fœtus, Ruffolo (1956) with a 28 weeks fœtus, Kohl (1960) with a 20 weeks fœtus and Goddard (1960) reported three cases with varying fœtal ages

Other cases were reported by Beltz & Hutchins (1951), Acosta Sison (1954), Taylor (1957), Waters & Grunden (1943), Favreau & Belanger (1939), MacRae (1951), Cline (1946), and others

Case Report

F R (Hospital No 1842) Admitted on 5.4.1961 to Alexandria University Hospital (Chatby)

The patient was thirty-eight years female married for 15 years She had had seven full term normal labours the last one two years previously She claimed to have amenorrhea for four months and slight vaginal bleeding for few days before admission When first examined the pulse rate was 69 temperature 37 C B P 180/120 The urine contained albumin +++ There was marked œdema of the lower limbs and abdominal wall. The uterine fundus which was felt with difficulty because of the marked œdema, reached to the level of the umbilicus Identification of fœtal parts was impossible No fœtal heart sounds were audible Vaginal examination revealed a soft closed cervix through which moderate bleeding was visualised

A clinical diagnosis is of vesicular mole was based on the undue enlargement of the uterus and the associated signs of severe toxæmia A plain X ray and an assay of the gonadotropins in urine was intended but half an hour after the examination the patient was seized with a *severe attack of bleeding* and she expelled spontaneously a twenty weeks living male fœtus with a crown heal length 18 5 cm weighing 316 gm and looking normally developed The umbilical cord was attached to a discoid placenta 10 cm in diameter which showed no vesicular degeneration on naked eye examination. The expulsion of the fœtus was accompanied and followed by the expulsion of many vesicles and a big blood clot

However the spontaneous expulsion was incomplete and *digital evacuation* was undertaken More vesicles were removed and during the exploration of the uterus the site of the placental attachment was felt and localised to a small area to the left on the anterior wall otherwise the surface of the uterine cavity was smooth

Apart from slight bleeding and a low grade pyrexia the patient was perfectly well on discharge A male frog test on the second day after evacuation was positive in 1/200 dilution after two weeks it was positive with undiluted urine and negative in dilution Two months later the frog test was negative

Microscopic examination of the placenta showed *no vesicular degenera-*

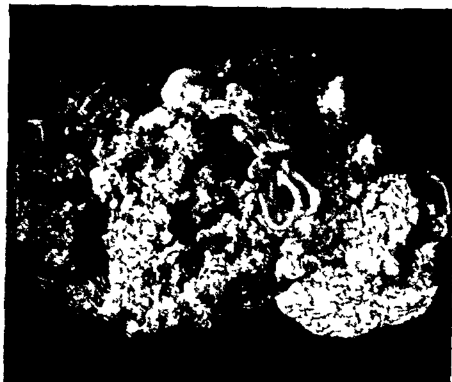


Fig 1 The fœtus, attached to a normal placenta to the right the vesicular mole in the centre and a big blood clot to the left.

tion. The fœtus showed no abnormal structures The vesicles showed the typical histological details of a vesicular mole

Fig 1 and Fig 2 show two photographs of the specimen

Discussion

The combination of a vesicular mole and well developed fœtus can result from

I Single ovum pregnancy with partial vesicular degeneration of the placenta (The transitional mole of Hertig & Edmonds)

II Double ovum pregnancy with vesicular degeneration and absorption of the fœtus in one ovum

III Simultaneous fertilisation of a normal ovum and a polar body undergoing molar degeneration



Fig 2 The fœtus connected to a normal (undegenerated) placenta

The presented specimen represents a double ovum rather than a single ovum pregnancy the microscopic identification of normal placental tissues attached to the umbilical cord and free from any vesicular degeneration confirms this diagnosis The chorionic plate was complete the amniotic sac was quite normal The associated signs of severe pre eclamptic toxæmia were the clue to the clinical diagnosis

SUMMARY

A case of vesicular mole with a twenty weeks living fœtus is presented The literature is reviewed and the possible ætiology is discussed The significance of associated severe pregnancy toxæmia in the clinical diagnosis of the case is stressed

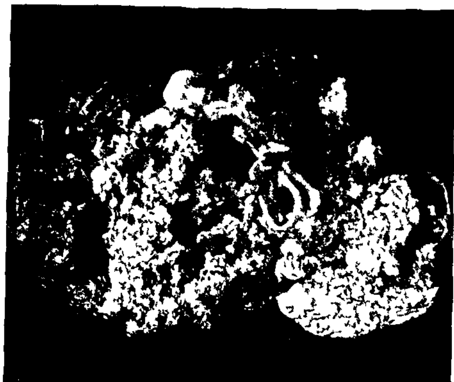


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Borell Ulf and Fernström Ingmar Acta obst. et gynec. scandinav 41 -13 196

From the Department of Diagnostic Rœntgenology (Professor Knut Lindblom) and the Department of Women's Diseases (Professor Ulf Borell) Karolinska Sjukhuset Stockholm Sweden

THE SHAPE OF THE FŒTAL CHEST DURING ITS PASSAGE THROUGH THE BIRTH CANAL A RADIOGRAPHIC STUDY

BY

ULF BORELL AND INGMAR FERNSTRÖM

As early as 1918 Warnekros made radiographic studies of the fœtal chest during its passage through the birth canal He observed that the fœtal chest was markedly compressed and elongated when the chest was passing through the muscles of the pelvic floor

Greenhill (1955) and Martius and Bickenbach (1956) confirmed this observation Their textbooks contain illustrations of the head immediately after expulsion which demonstrate the escape of amniotic fluid and mucus from the infant's respiratory tract These workers believed that this was due to compression of the chest, which at that stage still lies in the true pelvis

Olshausen (1901) expressed the view that respiration is initiated by the release from compression and consequent expansion of the chest immediately following its delivery As a result thereof air is drawn into the respiratory tract On the basis of his radiographic findings Warnekros supported this view

During intra uterine life amniotic fluid accumulates in the fœtal bronchi Compression of the chest immediately after delivery of the head would therefore be an ingenuous device of nature to clear the fœtal bronchi

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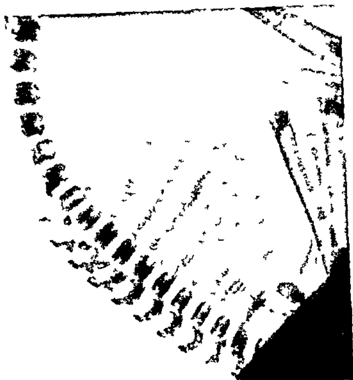


Fig 1 c Lateral view of the fœtal chest

ed with the thoracic spine was shown to be acuter as compared with that which the other ribs formed with the latter which was about 60° Immediately after the expulsion of the head practically the entire chest lay in the birth canal In the antero posterior films of the true pelvis taken at this stage the orientation of the fœtal chest was found to vary In 6 cases the transverse diameter of the chest coincided with the transverse diameter of the maternal pelvis the projection of the chest on the antero posterior films in these cases being antero posterior (Fig 2 a) In 6 cases the chest was partially rotated to give an oblique view on the antero-posterior film (Fig 2 b) In 3 cases the transverse diameter of the chest was in the antero posterior plane of the pelvis and it was



Fig 1 b Oblique view of the fœtal chest

Radiographic Findings

The shape of the fœtal chest as seen on the lateral films taken before the commencement of labour in the 100 cases is demon strated in Figs 1 a b and c As is seen the angle which the 11th and 12th ribs respectively formed with the thoracic spine was in all cases about 60° that which the other ribs formed with the latter being about 90°

In the films taken during labour the fœtal chest was seen to undergo compression throughout its passage through the true pelvis The angle which the 11th and 12th ribs respectively form

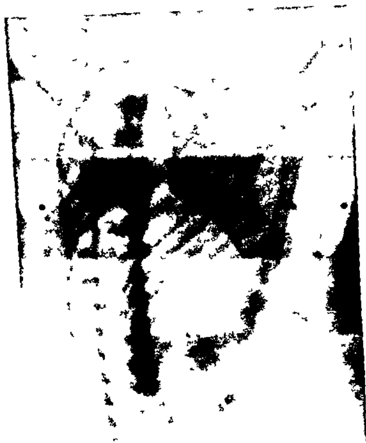


Fig 26 Oblique view of the fœtal chest

diameter was seen to be in a sagittal position and at a lower level the chest was found to have rotated the transverse diameter being in the oblique or transverse position

In the majority of cases the thoracic spine was found to be almost straight immediately after the birth of the head at this stage practically the whole chest lay in the true pelvis In a few cases the lower part of the cervical and the upper part of the thoracic spine was slightly flexed generally in the direction of the anterior wall of the birth canal



Fig 2 a Antero-posterior view of the fœtal chest

Fig 2 a b, c Antero-posterior film of the true pelvis taken during labour demonstrating the fœtal chest in the antero-posterior oblique and lateral projection respectively It is seen to lie in the birth canal and to be compressed The angle which the 11th and 12th ribs respectively form with the thoracic spine is acuter than that which the other ribs form with the latter which is about 60°

thus seen as a lateral projection on the antero posterior film (Fig 2 c)

With few exceptions the chest was found to rotate during its descent through the birth canal At the pelvic inlet the transverse

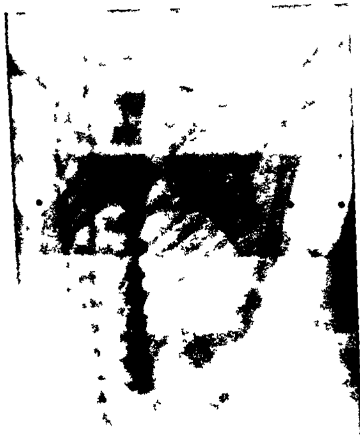


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Fig 2c Lateral view of the fœtal chest

Discussion

The findings in the present investigation confirmed Warnekros observation that the fœtal chest undergoes compression at the level of the muscles of the pelvic diaphragm and also demonstrated that the chest is compressed consistently throughout descent

The birth canal is curved forward and Warnekros believed

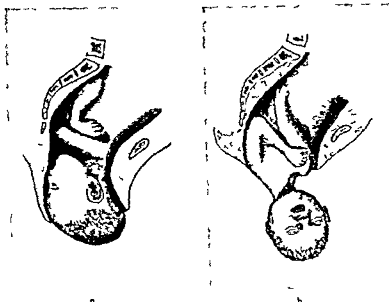


Fig 3 Schematic representation of the position and attitude of the fœtus and the course of the birth canal in the different stages of labour a the birth canal and the position and attitude of the fœtus when the head appears at the vulva b the birth canal and the position and attitude of the fœtus after expulsion of the head

that the shape did not undergo any changes during the different phases of expulsion If Warnekros view holds good the fœtal chest which often lies sagittally or obliquely in the birth canal, would therefore have to bend laterally in order to pass through the curve of the birth canal the part of the chest lying near the symphysis pubis being therefore compressed to a greater degree Warnekros believed that the antero posterior film of the true pelvis which demonstrates the chest to be in an oblique position furnishes evidence in support of this view However he did not study this point by simultaneous antero po terior and lateral radio graphy of the true pelvis the only method of examination available which affords reliable information

In a previous paper it was shown that immediately before ex pulsion of the head the birth canal is curved ventrally the angle

being about 90° The distal part is formed by greatly distended and elongated maternal soft parts (Borell and Fernström, 1957) Its long axis is curved ventrally in relation to that of the straighter, more proximal part of the birth canal Immediately after the birth of the head a lateral film of the true pelvis shows *the thoracic and cervical spine to be almost straight* This indicates that after the birth of the head the soft tissue part of the canal retracts resulting in the shortening and straightening of the whole birth canal (Fig 3) After the head has passed through the vulva the fœtal body is expelled in a purely distal direction and does not follow the distal and ventral course taken by the head

SUMMARY

The present investigation has shown that the fœtal chest is consistently compressed during its passage through the birth canal

The radiographic findings suggested that immediately after the expulsion of the head the shape of the birth canal differs from that generally described, *i e* the birth canal follows an almost straight course

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ALTERATION OF THE INFANT'S THORAX DURING VAGINAL DELIVERY

Physiological Studies[1]

BY

PETTER KARLBERG FORREST H ADAMS[2] FERNAND GEUBELLE[3] AND GÖRAN WALLGREN

In the preceding paper radiographic studies on infants during normal vaginal delivery were reported The results of these studies were interpreted to show that the infant s thoracic cage is considerably compressed during its passage through the birth canal but has essentially the same contour prior to this as it does following the establishment of pulmonary ventilation after delivery Earlier cine radiographic studies on newborn infants by our group have also shown no significant change in the shape of the thoracic cage between the very short period after delivery prior to the first breath and at end expiration of the earliest breaths (Geubelle *et al* 1959 Karlberg *et al* 1956) These findings have to be considered in relation to the fact that successful extra uterine existence of the newborn infant requires aeration of the lungs It has been suggested that compression of the thoracic cage during

[1] One of a series of studies supported by research grants from the Swedish Medical Research Council and from the Association for the Aid of Crippled Children New York City

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delivery and the subsequent elastic recoil is of importance for the initiation of this operation In order to obtain further information in this respect some functional studies have been performed in the period beginning with the presentation of the infant s face at the vulva and continuing until a few minutes after delivery of the body

Material

Sixteen spontaneous deliveries with the fœtus presenting by the vertex were studied The ages and parities of the mothers as well as the birth weights of the infants are given in Tables I and II The mothers were healthy and the pregnancy and labour was normal in all cases In general, no analgesia was used, but some of the mothers received nitrous oxide intermittently during the latter part of labour Light chloroform anesthesia was given when the head was crowned In no case was resuscitation of the infant required All newborn infants had a normal respiratory pattern within a few minutes and had a normal course during the neonatal period

Methods

In principle the technique and apparatus were the same as previously used in studies of the mechanics of breathing during the neonatal period (Karlberg *et al*, 1960) Pressure changes within the œsophagus were recorded by means of a waterfilled, open polyethylene catheter, 1 mm internal diameter Intra œsophageal pressure was considered representative of intra thoracic pressure (Karlberg *et al*, 1960) As soon as the infant s head was delivered the catheter was introduced through the nose The tip was advanced to a point approximately at the junction of the upper and middle third of the œsophagus The catheter was connected directly to an electromanometer (Elema) and the system was flushed with water prior to recording The amplified signals were recorded on a direct writing recorder (Elema Mingograph) In the calculations all pressures were corrected for possible hydrostatic influence

The volume was recorded using a reverse plethysmograph. A mask was placed tightly on the infant's face at the moment it appeared at the introitus. The mask was connected by tubing to an inflexible 35 litre plastic container. Respiratory volume changes caused by movements of gas and/or liquid produced a slight pressure change in the closed system and this was detected by an electromanometer. The amplified signals were recorded simultaneously on a Mingograph at two sensitivities.

The pressure and volume recordings reported in this study were not performed simultaneously for technical reasons. The recording period included the first few breaths but details of these results will not be reported here. The intra-œsophageal pressure recordings were performed in 11 infants, the volume recordings in 5.

Results

Intra œsophageal pressure. During delivery of the thorax there was a positive pressure of variable magnitude. A typical record is shown in Fig. 1 (infant 11). Immediately after delivery the

Table 1 *Recorded Intra-œsophageal Pressure Changes*

Case Number	Mother: Age	Mother: Parity	Birth Weight Grams	Intra-œsophageal Pressure: Before Delivery of the Body cm H_2O	During Delivery of the Body cm H_2O	After Delivery of the Body cm H_2O
1	26	I	3 030	44	95	0
2	41	I	2 680	19	22	0
3	20	I	3 670	20	59	0
4	31	II	4 170	—	60	0
5	36	V	4 130	39	60	—
6	25	III	3 220	—	75	—
7	30	I	3 9 0	42 14	36	0
8	33	IV	4 400	—	70	—
9	[illegible]5	II	3 700	14	41	0
10	37	IV	3 75[illegible]	14	46	0
11	38	I	2 880	14	84	0

Recordings began during delivery of thorax; pressures may have been higher before recordings began.

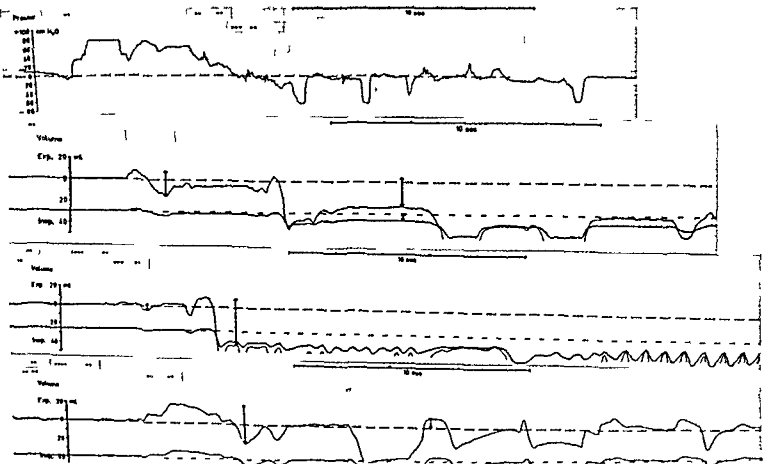


Fig 1 Pressure recording in one infant (number 11) and volume recordings in three infants during (numbers 13 16 and 15) delivery and the first breaths

pressure returned to zero Whenever possible three pressures were calculated from each record, the period between delivery of the face and the body, during the delivery of the body, and immediately after completion of the delivery (Table I)

Volume In each infant an inspiratory volume was recorded immediately after the delivery of the thorax (Table II) In the short

Table II *Respiratory Volume Changes*

Case umber	Mother		Infant	Inspiratory Volume Changes in ml.				Sum of (a) an (b)
	Age	Parity	Birth Weight in Grams	During Delivery of the Body (a)	Between Delivery and 1st Breath	During First Visible Breath (V_T)	Residual Volume After 1st Breath (b)	
12	27	II	3 400	29	—2	51	13	42
13	23	II	3 630	24	—19	48	27	51
14	29	I	3 100	7 + 11[1]		25	2	20
15	28	III	4 080	19 + 23[1]	—26	45	—7	35
16	32	I	4 6,0	7[2]	—16	76	50	57

[1] The inspiratory volume change during the delivery of the body continued for a few seconds but definitely ceased before the first visible breath

[2] During the delivery the mother ruptured the recto-vaginal septum.

period until the first visible breath there was often an expiratory volume change of varying magnitude Table II also shows the tidal volume of the first breath and the residual volume after the first breath, *i e* the difference between the inspired and expired volumes In Fig 1 volume recording of 3 infants during delivery are shown

Discussion

The positive intra-œsophageal pressures observed during the delivery of the thorax correspond well with directly recorded intra uterine pressures (Caldeyro Barcia and Poseiro 1959, Lindgren, 1959) Lindgren showed that the intra uterine pressure between contractions was 14 cm H O during contractions it rose to 65 cm H_2O and rose still further to 130–250 cm H O when the mother assisted contractions by bearing down Imme-

diately after delivery the intra-œsophageal pressure returned approximately to zero, *i e* equal to the atmospheric pressure These findings indicate that the elastic recoil of the thoracic cage is completed immediately after delivery of the thorax and before the first visible breath This is in agreement with previous observations from this laboratory (Karlberg *et al*, 1962) in which no consistent negative pressure was recorded before the first visible breath

The marked compression ("squeeze) of the infant during delivery does increase the intra-thoracic pressure considerably (Table I) Once the head is delivered a pressure difference between the mouth and the thorax is created which would serve to express the amniotic fluid from the airways This reasoning seems in agreement with the clinical observation that fluid flows out of the nose and mouth, sometimes as a jet, at this stage of delivery Even though the technique used in this investigation permitted only the last part of the delivery to be studied in regard to pulmonary volume changes, expiratory volumes of as much as 20 ml were recorded during the latter part of the passage of the fœtus through the birth canal

When the body is delivered the thorax recoils towards its former shape and in so doing the volume lost during the squeeze tends to be replaced That such a passive inspiratory movement occurs is shown by the fact that at this stage of delivery inspiratory volumes of as much as 29 ml were recorded (Table I) Taking into consideration that the functional residual capacity in a newborn infant with well established lung function is about 100 ml (Berglund and Karlberg, 1956 Geubelle *et al*, 1959) the æration preceding the first breath must be of significance The importance of the elastic recoil of the thoracic cage for æration of the lungs may be indicated by the inverse relationship between elastic recoil volume and the residual volume caused by the first breath, *i e*, the difference between inspiratory and expiratory volumes (see table II) Where the volume sucked in by the elastic recoil is big, there is a small residual volume after the first spontaneous breath and vice versa However, there is evidence that other supporting mechanisms may be present in the period before the first breath For example, active laryngopharyngeal move-

ments, observed by Bosma and Lind (Bosma et al , 1959), may contribute to the drainage of the amniotic fluid and to the aeration of the respiratory tract by forcing air into the trachea (by glossopharyngeal or frog breathing)

Because the intra thoracic pressure variations during vaginal delivery appear to play a role in facilitating the subsequent aeration of the lung parenchyma, it may be speculated upon whether the absence of the squeeze in infants delivered by Cæsarean section may at least in part, be responsible for the higher incidence of neonatal respiratory complications occurring in this group

SUMMARY

Intra-œsophageal pressure recordings in newborn infants during the delivery of the body and continuing during the first breath indicate that the thorax is compressed during its passage through the birth canal and that elastic recoil of the thorax occurs immediately after delivery Respiratory volume recordings during the same period indicate that the thoracic recoil may result in an appreciable contribution to the æration of the respiratory tract of the newborn infant

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THE VALUE OF CERCLAGE OF THE UTERINE CERVIX BY SHIRODKAR'S METHOD IN THE TREATMENT OF HABITUAL ABORTION

BY

CARL OLOF DANIELSON

The view has been expressed that insufficiency of the uterine cervix and isthmus associated with an abnormally wide internal os, accounts for many cases of habitual abortion (Palmer, 1950, Asplund, 1954, Bergman, 1958, Bergman, Genell and Wahlen, 1954) Cervical and isthmic insufficiency may be due to scar formation following mechanical trauma such as vaginal hysterotomy or dilatation of the cervix, or to hormonal or neurogenic disturbances

Two surgical methods have so far been recommended for the treatment of insufficiency of the cervix and isthmus One method is isthmorraphy, which results in re-establishing the normal width of the internal os and upper part of the cervical canal The operation consists of excising a wedge-shaped piece of the uterine wall at the assumed level of the internal os and stitching the edges of the wound together, the internal os being thereby narrowed Bergman *et al* (1954) treated a series of cases by this method and found it to be of great value in re-establishing the function of the isthmus Patients thus treated are more likely to carry subsequent pregnancies to viability and to deliver a living child According to these workers the operation should not be carried out during pregnancy

The second method was described by Shirodkar in 1951 It consists of placing a firm suture round the cervix at the assumed

level of the internal os He performed this operation on pregnant women who previously had had several abortions assumed to be due to insufficiency of the isthmus, and reported that many of them carried their existing and subsequent pregnancies to viability and were delivered of living children Several workers have used this method in the treatment of such cases (McDonald, 1957, Johnstone, 1958, and others)

If the operation is performed *lege artis* and in carefully selected cases, a large number of pregnancies which would have terminated in abortion or premature labour, proceed to viability and the delivery of living children

After the above method had been published it was reported that it could successfully be used in the treatment of threathened abortion and premature labour Bergman (1958), for instance, performed cerclage of the cervix on a patient in whom labour threatened at the 29th week of pregnancy, the cervix admitting the thumb After the operation the patient was kept in bed and seven weeks later she was delivered of a healthy child, weighing 2,580 g

Present Series

The series comprises 14 cases Twelve of these were treated in this Department and the remaining 2 in the Women's Clinic of the St. Erik's Hospital in Stockholm

In 5 cases cerclage of the cervix was performed during the acute stage *i e* in the presence of hæmorrhage and labour pains (Table I) In these cases the operation was undertaken to determine whether the procedure was of any value in such circumstances Four of these patients had a history of repeated abortions and in all of them the cervix was slightly dilated during pregnancy As all were anxious to have a living child they were willing to give a trial to any possible method of treatment

In the remaining 9 cases the operation was performed in the quiescent stage *i e* in the absence of symptoms of threatened abortion (Table II) All these patients had a history of repeated abortions and of confirmed or suspected insufficiency of the cervix and isthmus

Table I *Results of Cerclage of the Uterine Cervix Performed on Patients Showing Symptoms of Impending Abortion*

Hospital Rec No and Age of Patient	Obstetric History (Chronologically Reported)	Condition of Cervix and Isthmus before Pregnancy	Condition of Cervix and Isthmus during Present Pregnancy	Month of Pregnancy in which Cerclage was Performed	Post-operative Course of Pregnancy
360523 23 years	4 abortions each at 4th month	Widened internal os verified by HSG performed in the secretory phase Isthmorrhaphy	Slightly dilated	4th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 48 hrs after the operation
220616 36 years	3 normal deliveries, 1 vaginal hysterectomy 1 premature delivery of a non viable infant	No information available	Slightly dilated	5th	Operated upon a few days after the appearance of symptoms of impending abortion Hæmorrhage and slight pain Aborted 6 weeks after the operation The suture round the cervix had untied Non viable fœtus
321223 26 years	Primigravida	No information available	Slightly dilated	5th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 5 days after the operation The suture had cut through the cervix
270402 years	1 normal delivery 4 premature deliveries of non viable infants, 4 abortions each at 4th month	Widened internal os verified by Hegar's dilators in the secretory phase Isthmorrhaphy	Slightly dilated	4th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 24 hrs after the operation
0412 years	1 vaginal hysterotomy 2 abortions each at 4th month	No information available	Slightly dilated	4th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 3 days after the operation

= Hysterosalpingography

Hospital Reg. and Age of Patient	Obstetric History (Chronologically Reported)	Condition of Cervix and Isthmus before Present Pregnancy	Condition of Cervix and Isthmus during Present Pregnancy	Month of Pregnancy in which Cerclage was Performed	Postoperative Course of Pregnancy and Labour and Birth Weight of Infant
341302 [illegible] years	2 premature deliveries of non viable infants 1 abortion at 2nd month	No information available	Abnormally widened at 4th month	4th	Slight bleeding 6 weeks after the operation Labour uneventful Living child 2 750 g
[illegible]709 [illegible] years	1 normal delivery 1 Cæsarean section (placenta praevia) stillbirth 2 abortions at 2nd month respectively	Abnormally widened verified by HSG and Hegar's dilators	Slightly widened already at 2nd month	2nd	Uneventful Living child 2 780 g
350709 25 years	2 abortions at 4th and 5th month respectively	Normal verified by HSG	Admitted a finger at 4th month	4th	Uneventful Living child 3 350 g
341 07 26 years	2 abortions at 2nd month respectively 1 premature delivery of a non viable infant	Normal verified by Hegar's dilators	Almost admitted a finger at 4th month	4th	Uneventful but pregnancy terminated in premature delivery of a healthy living infant 2 480 g
180419 42 years	3 abortions at 5th 3rd and 4th month respectively	No information available	Abnormally widened at 4th month	4th	Uneventful Delivery by Cæsarean section because of age of patient and obstetric history Living child 3 300 g
290118 32 years	3 abortions at 3rd 4th and 3rd month respectively	Normal verified by HSG	Hemorrhage at 2nd month Almost admitted a finger at 4th month	4th	Uneventful Delivery by Cæsarean section because of breech presentation Living infant 3 740 g
60312 35 years	abortions at 3rd and 5th month respectively	Abnormally widened verified by HSC and Hegar's dilators	Hemorrhage at 2nd month Admitted a finger at 4th month	4th	Uneventful Living infant, 2 970 g
200305 31 years	4 abortions at 3rd 4th 2nd and 5th month respectively	Normal verified by Hegar's dilators	Widened to the width of a lead pencil at 4th month	4th	Hypertonia otherwise pregnancy uneventful but terminated in premature delivery of a healthy living infant 2 030 g
291106 32 years	3 abortions at 4th 2nd and 3rd month, respectively	Normal verified by Hegar's dilators	Almost admitted a finger at 4th month	4th	Uneventful Living infant 3 030 g

• HSG = Hysterosalpingography

Table I *Results of Cerclage of the Uterine Cervix Performed on Patients Showing Symptoms of Impending Abortion*

Hospital Rec No and Age of Patient	Obstetric History (Chronologically Reported)	Condition of Cervix and Isthmus before Pregnancy	Condition of Cervix and Isthmus during Present Pregnancy	Month of Pregnancy in which Cerclage was Performed	Post-operative Course of Pregnancy
360523 23 years	4 abortions each at 4th month	Widened internal os verified by HSG* performed in the se cretory phase Isth morrhaphy	Slightly dilated	4th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 48 hrs after the ope ration
220616 36 years	3 normal deliveries, 1 va ginal hysterectomy, 1 pre mature delivery of a non *viable infant*	No information available	Slightly dilated	5th	Operated upon a few days after the appearance of symptoms of impending abortion Hæmorrhage and slight pain Aborted 6 weeks after the operation The suture round the cervix had un tied Non viable fœtus
321223 26 years	Primigravida	No information available	Slightly dilated	5th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 5 days after the ope *ration* The suture had cut through the cervix
170402 3 years	1 normal delivery 4 pre mature deliveries of non viable infants 4 abortions each at 4th month	Widened internal os verified by Hegar s dilators in the se cretory phase Isth morrhaphy	Slightly dilated	4th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 24 hrs after the ope ration
40412 6 years	1 vaginal hysterotomy 2 abortions each at 4th month	No information available	Slightly dilated	4th	Operated upon a few days after the appearance of symptoms of impending abortion Aborted 3 days after the ope *ration*

SG = *Hysterosalpingography*

much more likely that the manipulations involved in the operation intensify them

All these patients were given progesterone therapy and sedatives pre operatively and post-operatively which might have contributed towards delaying abortion

Table II shows the cases in which the operation was performed during the quiescent stage In these instances the procedure appears to have been effective The argument may be raised that these patients would also have gone to term without being operated upon Considering their past histories, however, this does not seem likely Moreover, they all showed clinical symptoms, and many of them also radiological signs, of insufficiency of the cervix and isthmus It should also be mentioned that two of these patients attended because of signs of impending abortion, *i e* labour pains and bleeding Following cerclage of the cervix, performed four weeks later, both went to term and produced living children

All these patients were given a course of progesterone (Proluton depot 250 mg) therapy prior to and after the operation but were not kept in bed for prolonged periods either before or after the procedure They had all been treated with progesterone and rest in bed on the occasion of previous threatened abortions but without success It may therefore reasonably be assumed that cerclage of the cervix contributed towards the pregnancies progressing normally with the delivery of a living child It is interesting to note that 8 of these patients had never delivered a living child before the operation

Investigation of the patients included determination of the Rh factor and the Wasserman reaction In addition the husband's seminal fluid was examined However none of these tests afforded any information as to the cause of the patient's tendency to abort

Discussion

The diagnosis of insufficiency of the cervix and isthmus should not be too readily There are cases termed by Eastman (1956) "physiological incompetent cervix" in which the cervix is found to be slightly dilated during pregnancy but the pregnancy con

Method

The operation is carried out under general anæsthesia with the patient in the lithotomy position The vagina is cleansed and the anterior and posterior lips of the portio are grasped with ovum forceps and gently drawn downward A transverse incision, 2 to 3 cm long, is then made, about 2 cm above the anterior lip of the portio and the urinary bladder is gently dissected free so as to give access to the upper part of the cervix and the region of the internal os A thick nylon thread or nylon ribbon is inserted round the cervix under the mucosa and carried to the posterior fornix, using a Deschamps' needle or an ordinary strong surgical needle Another incision is then made in the mucosa of the posterior fornix through which the nylon thread ribbon is carried forward under the mucosa on the other side of the cervix to the anterior incision The nylon thread or ribbon is knotted but not tighter than will permit the introduction of a No 5 or 6 Hegar s dilator into the cervical canal The suture round the cervix is fixed to the uterine wall by silk suture The vaginal mucosa is then sutured with catgut

The patient is kept in bed for one or two days prior to, and five or seven days after the operation If no symptoms of threatened abortion appear, she is then allowed up and about throughout her pregnancy

About two weeks before full term or after the commencement of labour the suture round the cervix is removed through an incision in the vaginal mucosa Anæsthesia is generally not required for this procedure, nor is it necessary to suture the incision after delivery

The operation is technically comparatively easy It may be difficult to insert the suture sufficiently high on the cervix In some cases it was not possible to apply it higher than just below the level of the internal os Nevertheless, even in these cases the operation appeared to be effective

Table I shows the cases in which the operation was carried out in the acute stage The results show that it was hopeless to try to check the expulsion of the conceptus by cerclage of the cervix This procedure does not inhibit uterine contractions It is

be carried out early, i e between the 2nd and 3rd months of pregnancy

As already mentioned, cerclage of the cervix is a relatively easy procedure All the patients in this series operated upon in the quiescent stage went to term after the operation and were delivered of living children

A careful follow up of the patient after the operation is imperative If she develops symptoms of threatened abortion or premature labour she must immediately be admitted to hospital If these do not respond to conventional treatment, the suture round the cervix must be removed

SUMMARY

Cerclage of the uterine cervix according to Shirodkar's method was performed in a series of 14 cases of habitual and impending abortion All these patients were operated upon during pregnancy and had symptoms and signs of insufficiency of the cervix verified clinically or by radiography

In 5 cases the operation was performed a few days after symptoms of impending abortion had appeared and was ineffective In the remaining 9 cases it was carried out in the absence of symptoms All these patients went to term and produced living children Eight of them had failed to carry or deliver a live child in pregnancies preceding the operation

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tinues to viability and a living child is delivered In such cases cerclage is, of course, contra-indicated On the other hand, if the cervix admits a finger between the 3rd and 5th months of preg nancy and there is a history of repeated abortions and/or pre mature labour the diagnosis can be made with confidence and operation is indicated Careful analysis of the past history is helpful in differentiating between these two types of case

When examining a non-pregnant woman it should be borne in mind that the size of the cervical canal varies in the different phases of the menstrual cycle, it is wider in the proliferative phase than in the secretory phase (Asplund, and others) If the internal os easily admits a No 8 Hegar's dilator in such cases, insufficiency is strongly suggested but operation is not indicated unless there is a history of repeated abortions and/or premature births

Hysterosalpingography is often of value in establishing the diagnosis of insufficiency of the cervix and isthmus in non pregnant women Moreover, this method of examination also reveals sub mucous myomata or malformation of the uterus, con ditions which, if present, may account for the patient s tendency to abort

Although the series of cases presented is small, the results indicate that cerclage of the cervix performed for certain well defined indications may be effective in the prevention of habitual abortion or premature labour If a pregnant patient has a history of repeated abortions, and insufficiency of the cervix and isthmus is verified, this method of treatment should be given a trial The operation should be carried out in the quiescent stage, *i e* be- fore symptoms of impending abortion appear If they are present, the ordinary therapeutic measures should be given a trial first If they are effective and there is convincing evidence that the pregnancy progresses normally, cerclage of the cervix can be per formed later

It has been reported that the best results are achieved if cerclage of the cervix is performed during the 4th and 5th months of pregnancy However, the choice of the time for the operation depends largely on the past history in the individual case If pre vious abortions occurred early in pregnancy, the operation should

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Hofbauer *et al* (1927), like others (Slemons 1932, Morton 1933, Holmes 1934) administered oxytocin intranasally In diabetes insipidus vasopressin administered in this way is rapidly absorbed On intranasal administration of oxytocin, however, with the technique used the effect was uneven and unreliable Over dosage was common, and the method was abandoned

In a preliminary investigation (Borglin 1961) oxytocin was given intranasally in a modified form and proved to give better results Recently Baumgarten and Hofhansl (1961) showed in addition that oxytocin given by nasal spray can be used as a test for demonstrating that the uterus is prepared for labour

This paper is concerned with the results of induction and stimulation of labour with oxytocin intranasally in a larger series

The Series and Methods

The effect of oxytocin given intranasally was compared with that obtained when the hormone was given by intravenous drip All of the patients in whom labour was induced or stimulated in the Department during the period January–August 1961 are included in the present investigation The total number of deliveries and the number of patients treated with oxytocin are given in Fig 1 The total number of women delivered during this period was 2316 132 of them had received oxytocin by intravenous drip, 96 by the intranasal route and 4 by one route on one occasion and by the other route on a later occasion The age distribution and parity of the patients are given in Table I In a few cases oxytocin was first given intranasally during April as a preliminary trial From June on the intranasal route was used with increasing frequency and during July and August is was the only route used

Oxytocin drip was given according to the routine method of the Department in a cubital or forearm vein The concentration of the solution was 1 I U per 100 ml 5 5 % glucose If this concentration proved insufficient the dose was increased to 2 I U *per 100 ml* 5 5 % glucose occasionally 4 I U were used with the same amount of glucose The drip rate which was initially 10–15 was successively increased to 40–50 drops per minute If this

Borglin N E Acta obst et gynec scandinav 41 238 196_

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INTRANASAL ADMINISTRATION OF OXYTOCIN FOR INDUCTION AND STIMULATION OF LABOUR

BY

N E BORGLIN

During the last 40 years oxytocin has been widely used for inducing and stimulating labour Since the hormone is destroyed in the digestive tract, it has to be given sublingually, intranasally or parenterally in the form of subcutaneous, intramuscular or intravenous injections or by intravenous drip

Of these forms of administration, only the intravenous drip (Theobald *et al*, 1948) has proved effective and fairly safe The results obtained by this method in Sweden have been described by von Friesen (1954), Engstrom and Ohlson (1956) and Engstrom (1959) However, intravenous drip has certain disadvantages it confines the patient to bed, it requires the attendance of a trained nurse, and many patients find it very disagreeable A transient increase in the rate of infusion carries a risk of uterine tetany and thereby of fœtal asphyxia

Owing to these disadvantages attempts have been made to give oxytocin by other routes In recent years the sublingual and the transbuccal administration (Donaldson 1920, Hamill 1920, Knaus 1926) have been tried again (Dillon *et al* 1960, Rice and Benson 1961), but the results cannot be regarded as good, and it often requires large doses of oxytocin, on the average 1,000 to 2,000 I U The amount of the hormone absorbed must be very low, the absorption uneven and unreliable, and it is probably impossible for the patient to avoid swallowing the major part of the dose, which is thereby rendered ineffective



Fig 2 (a) Equipment for administration of oxytocin intranasally Polyethylene tube graded for 0 1 ml and 0 2 ml and the bottle of oxytocin containing 2 ml of solution (100 IU/1 ml) (b) Illustrates how polyethylene tube is filled with desired amount of the solution

The concentration of the solution used for intranasal administration varied during the period of the investigation Initially a solution containing 50 I U per ml was used then 150 I U per ml and later we found a concentration of 100 I U per ml to be most suitable This concentration was used in the majority of the cases The composition of the solution was as follows

Oxytocin	(50) 100 (150) I U
Natr chlor	0 009 g
Chlorbutol	0 003 g
Aqua redest	ad 1 ml

The oxytocin used in this solution was the chromotographically isolated pure octapeptide prepared from hog hypophysis The solution was administered by a polyethylene tube with an inner diameter of 2 and an outer diameter of about 4 mm The patients were instructed to blow the entire dose into one of the nasal cavities The tube was graded in 0 1 and 0 2 ml and it was not

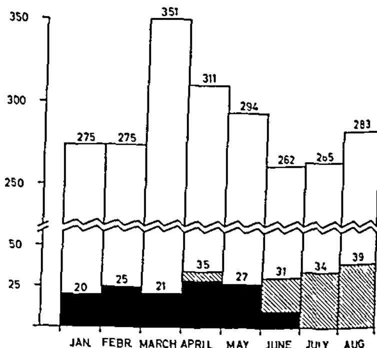


Fig 1 Number of deliveries per month and number of cases treated with oxytocin by intravenous drip (filled areas) or intranasally (hatched areas)

Table I *Age Distribution and Number of Primigravidæ and Multigravidæ in the Different Groups*

Age in Years	Oxytocin Intravenous		Oxytocin Intranasal		Oxytocin Intravenous and Intranasal		Total
	Primigravidæ	Multigravidæ	Primigravidæ	Multigravidæ	Primigravidæ	Multigravidæ	
–19	2	–	2	1	–	–	5
20–24	24	1	22	3	1	–	51
25–29	36	12	24	3	1	1	77
30–34	17	11	10	16	–	–	54
35–39	13	9	6	6	–	1	35
40–	1	6	1	2	–	–	10
Total	93 (70 5 %)	39	65 (67 7 %)	31	2	2	232
	132		96		4		

rate infusion failed to produce the desired effect, the concentration of the solution was increased The patients were rarely out of bed during the infusion They were supervised by trained nurses

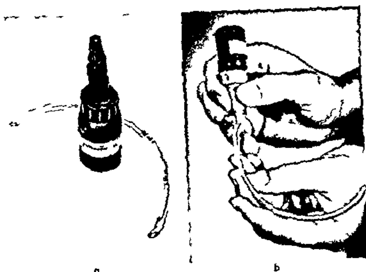


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difficult to measure off a quantity of exactly 0 05 ml (Fig 2) The patients could thus be given a dose of 5-40 I U (solution containing 100 I U/ml) When the 0 4 ml dose was used, 0 2 ml was given into each nasal cavity When more than 0 2 ml was given into one nasal cavity, some of the solution could flow down into the throat Rarely was the largest dose, 40 I U, administered

If the dose given exerts any effect, it does so within 2-5 minutes and lasts for 15-30 minutes, rarely longer We always began with a dose of 0 05 ml and adjusted further dosage according to the effect of the previous dose If the dose produced no effect, the second was not given until after an interval of 15 minutes The dose was then gradually increased After some doses of 0 05 ml we gave 0 1 ml on a few occasions, and, if necessary, 0 2 ml Unless confined to bed for other reasons, the patients were allowed to be up and about without any extra attendance

The general management in other respects was the same throughout the entire period of the investigation Enema, castor oil and artificial rupture of the membranes were often used to induce labour The frequency with which the membranes were ruptured in the two series is detailed in a later section

Results

The results are given in Table II The results were said to be successful only when delivery was completely unaided

Of the group that received oxytocin by intravenous drip 85 per cent were delivered after the first treatment (81 per cent of the primigravidæ and 95 per cent of the multigravidæ) The corresponding figures for the group that received oxytocin intra nasally were 79 per cent, 74 per cent and 90 per cent Of the 9 women, all primigravidæ who required a second intravenous drip, the effect was satisfactory in 8 Of the 11 women who received a second course by the intranasal route (9 primigravidæ and 2 multigravidæ) the effect was satisfactory in 7 of the primigravidæ and in the 2 multigravidæ

The interval between the beginning of the treatment and the birth of the child is given in Table III This table includes only

Table II *Results of Oxytocin by Intravenous Drip and Oxytocin Intranasally on Consecutive Days*

Method	Day	Primigravidæ			Multigravidæ			Primigravidæ and Multigravidæ		
		Total Number of Cases	Successful		Total Number of Cases	Successful		Total Number of Cases	Successful	
			No			No	%		No	
Intravenous drip	I	93	75	80 6	39	37	94.8	132	112	84.8
	II	9	8	88 9	–	–	–	9	8	88 9
Total			83	89 2		37	94 8		120	90 9
Intranasal application	I	65	48	73 8	31	28	90 3	96	76	79 2
	II	9	7	77 8	2	2	100	11	9	81 8
Total			55	84 6		30	96 8		85	88 5

Table III *Duration of Labour Calculated from the Beginning of Treatment with Oxytocin until Delivery of the Child Only Those Patients are Included Who Are Shown in Table II and Were Delivered after a Single Course of Treatment*

Time in Hours	Intravenous Drip		Intranasal Application	
	Primigravidæ	Multigravidæ	Primigravidæ	Multigravidæ
– 2	15	11	12	4
2– 4	21	9	14	9
4– 8	24	17	8	11
8–16	14	–	13	4
16–24	1	–	1	–
Total	75	37	48	28

those women who were delivered after a single course of treatment It will be seen from the table that about 50 per cent of the women were delivered within 4 hours

The indications for oxytocin therapy are given in Table IV The indications were largely the same in both groups On the other hand the two groups differed considerably regarding pre

Table IV *Indications for Oxytocin*

Indications for Oxytocin	Oxytocin Intravenous	Oxytocin Intranasal	Oxytocin Intravenous and Intranasal	Total
Presumed postmaturity	20	13	1	34
Rh sensitization	7	1	–	8
Toxæmia of pregnancy	5	3	–	8
Intrauterine death	4	1	–	5
Primary uterine inertia	86	71	3	160
(and early rupture of membranes)	(70)	(50)	(3)	(1 3)
Secondary uterine inertia	6	2	–	8
Other indications	4[1]	5[2]	–	9

[1] Placenta prævia 2
Diabetes mellitus 1
Chronic nephritis 1
4

[2] Placenta prævia (Cæsarean section in one case) 3
Contracted pelvis delivery started at term 1
Chronic nephritis 1
5

Table V *Obstetric Status before Treatment with Oxytocin Was Started*

Level of Presenting Part of Fœtus	Intravenous Drip			Intranasal Application		
	Membranes Intact	Membranes Ruptured	Total	Membranes Intact	Membranes Ruptured	Total
At most at midplane	20	86	106 (80.3%)	33	53	86 (89.6%)
Below midplane	4	22	26	1	9	10
No labour	8	40	48 (36.4%)	9	34	43 (44.8%)
Labour	16	68	84	25	28	53
Total	24 (18.2%)	108	132	34 (35.4%)	62	96

vious rupture of the membranes position of the presenting part of the fœtus in the pelvis, and incidence of labour before treatment with oxytocin (Table V)

Table VI Birthweights

Birthweights g	Oxytocin Intravenous	Oxytocin Intranasal	Oxytocin Intravenous and Intranasal	Total
–1 499	–	1	–	1
1 500–1 999	2	–	–	2
2 000–2 499	1	1	–	2
2 500–2 999	15	11	1	27
3 000–3 499	44	39	–	83
3 500–3 999	48	23	3	74
4 000–4 499	17	15	–	32
4 500–4 999	2	3	–	5
5 000–	1	1	–	2
Twins	2	2	–	4
	132	96	4	232

The foetal membranes were intact in 18 2 per cent of the group that received oxytocin drips, against 35 4 per cent of the group treated intranasally

At the start of oxytocin infusion the presenting part of the foetus was above the midplane in 80 3 per cent the corresponding figure for the group treated intranasally being 89 6 per cent Of the group treated with oxytocin drip labour was induced in 36 4 per cent The corresponding figure for the group treated with oxytocin intranasally was 44 8 per cent

The birth weights of the infants are given in Table VI In 2 of the group treated with oxytocin intranasally it was less than 2 500 g In one of them labour was induced 2 months before calculated term because of known foetal death and in the other the patient was admitted to the Department because of slight labour with escape of amniotic fluid at presumed term Labour was stimulated and the patient was delivered about 2 hours later The child weighed 2 460 g and was healthy Three of the children in the group treated with oxytocin intravenously weighed less than 2 500 g In 2 of the cases labour was induced becauses of foetal death These two stillborns weighed 1,550 and 1 700 g respectively In the third case the patient hade been admitted because of bleeding 6 weeks before calculated term It was suspected and later proved that the bleeding was due to lateral placenta

Table VII *Presentation of Fœtuses*

Presentation of Foetuses	Oxytocin Intravenous	Oxytocin Intranasal	Oxytocin Intravenous and Intranasal	Total
Occiput anterior	116	80	3	199
Occiput posterior	2	8	–	10
Breech	12	4	1	17
Brow[1]	–	(1)	–	(1)
Cæsarean section	–	2	–	2
Twins	2	2	–	4
	132	96	4	232

[1] Cæsarean section

Table VIII *Treatment for Induction or Stimulation of Labour and Operative Procedures to Complete Delivery*

Procedure	Oxytocin Intravenous	Oxytocin Intranasal	Total
Oxytocin only	95 (72 %)	77 (80 %)	172
+ VE forceps or breech extraction	7	7	14
+ rupture of membranes	25	9	34
+ + VE	4	1	5
+ perineotomy because of fœtal asphyxia	1	–	1
+ Cæsarean section	–	2	2
Total	132	96	228

prævia The membranes were therefore ruptured after which oxytocin drip was started The child, which weighed 2,320 g, was delivered with the aid of a vacuum extractor because of threatened fœtal asphyxia Respiration was impaired after delivery and the child died aged 12 hours

The presentations of the infants are given in Table VII Immediately before or during oxytocin therapy the membranes were artificially ruptured in 29 of the women in the group that received oxytocin drip and in 10 of the group that received oxytocin intranasally These and other operative procedures used at delivery are detailed in Table VIII

Table IX Compl cations d r ng Del ery and Parturit on

Fœtal Comp ica ions	Oxytocin Intravenous	Oxytocin Intranasal	Total
Irregular fœtal heart sounds (a/)	12	10	22
Asphyx a dur ng or immed ately after partur tion (b/)	5	5	10
a/ and b/	4	3	7
	16 %	19 %	
Premature separat on of placenta	(1)[1]		(1)
Fœtal death poss bly due to therapy	5[2]		5
No comp cat ons	106 (80 %)	78 (81 %)	184
Total	132	96	228

[1] In 2 cases w th uter ne tetany
[2] See text

The complications are summarized in Table IX The frequency of compl cations was roughly the same in both groups Delivery was uncomplicated in 80 per cent of the cases treated with oxy tocin ntravenously and in 81 per cent of the group that received oxytocin intranasally The most severe complications occurred in the former group with 5 stillbirths partly or entirely ascribable to the infusions In a further case abruptio placentæ was diagnosed In 2 of the cases treated with oxytocin intravenously uterine tetany occurred In the group that received oxytocin intranasally there were no fœtal deaths due to the treatment no premature separat on of the placenta or uterine tetany The maternal mor tal ty was n l in both groups

The de a ls of the severe compl cations in the group treated w th oxytocin intravenously were as follows

1 44/61 A 35 year old primigravida was admitted thought to be beyond term in weak labour with intact membranes F ve days after adm ssion the membranes were ruptured and an oxytocin drip was started About 6 hours la er uterine tetany s ddenly occurred and the fœtal heart sou ds became irregular The dr p was immed ately stopped oxygen was gi en and the ch ld was extracted with forceps The ch ld had a facial paralysis but was l ter e normal

2 1481/61 A 30 year old Gravida II whose first child was two years old. During her previous pregnancy she had had hypertension which had persisted. On admission she was probably beyond term After the membranes had been ruptured oxytocin drip (1 IU/100 ml in 5.5% glucose) was started Despite a comparatively slow rate of infusion the treatment resulted immediately in uterine tetany and treatment was stopped The fœtal heart sounds were irregular and the liquor amnii was discoloured Moderate labour continued and the patient was delivered after about 1 hour The child was normal

3 384/61 A 34 year old primigravida, who was admitted at term in weak labour and draining liquor Oxytocin drip had a moderate effect. About 1 hour after the beginning of the infusion the fœtal heart sounds became irregular and symptoms of premature separation of the placenta appeared. The presenting part of fœtus was 2–3 fingerbreadths from the pelvic outlet and the cervix was fully dilated Delivery was completed with the vacuum extractor The child weighed 4 120 g it was asphyxiated but responded to resuscitation The diagnosis of abruptio placentæ was confirmed

4 413/61 A 31 year old primigravida admitted at term in weak irregular labour which persisted unchanged during the following days Oxytocin drip was started The membranes ruptured spontaneously after 4 hours Five hours after this the fœtal heart sounds ceased The presentation was occipito-anterior, and despite immediate extraction (vacuum extractor) the child (weight 3 400 g) was dead *Post mortem* examination showed intrauterine asphyxia as the cause of death

5 472/61 A 25 year old primigravida was admitted in weak labour beyond term Rœntgen examination showed that the fœtus was large The membranes were ruptured and oxytocin drip was given The fœtus was in the occipito-anterior presentation and was delivered after 6 hours The child (weight 5 700 g) was asphyxiated and died 36 hours later Necropsy showed signs of intrauterine aspiration and also malformations (deformation of the face with macrostomy)

6 640/61 A 27 year old primigravida admitted at term draining liquor and in weak labour was given an oxytocin drip After 10 hours and 20 minutes the child which was presenting by the breech was delivered (weight 4 700 g) It was asphyxiated and died 4 hours later because of aspiration

7 734/61 A 38 year old Gravida III (children born in 1945 and 1958 without complications) was admitted 6 weeks before the expected date of delivery because of bleeding and weak labour The bleeding was due to partial placenta prævia After rupture of the membranes oxytocin was given by intravenous infusion, with moderate success The child was in the occipito-anterior presentation Owing to fœtal asphyxia it was delivered by vacuum extractor The child (weight 2 320 g) was asphyxiated and died after 12 hours Necropsy showed immaturity hyaline membrane and hypoxia (This case is also included in the discussion above on the birth weights of the children)

Table X. *Loss of Blood n Assoc at on with Del very*

Bleeding before and a Delivery	Oxytocin In ravenous	Oxytocin Intranasal	Oxytocin Intravenous and In ranasal	Total
100 ml	9	10	–	19
101 200	81	62	3	146
201 400	34 94 %	13 89 %		47
401–600	6	5	1	12
> 600	2	4[1]	–	6
Cæsarean sect on	–	2		2

750 and 825 ml

[1] 700 900 1 420 and 1 500 ml

8 845 61 A 31 year old prim gravida was admitted ad term in weak labour dra n ng liquor The breech was present ng An oxytoc n drip was g ven The fœtus (we ght 3 6 0 g) was del vered after 5 hours 20 minutes Dur ng labour no s gns of fœtal asphyxia were observed but the child was born dead Necropsy revealed pulmonary hæmorrhages The obstetr cian suspected premature separat on of the placenta because of the infus on but this was not confirmed

During or immediately after the delivery 0 2 mg of methyl ergobasin maleinate was given intravenously (1 ml Methergin Sandoz) as is done routinely at all deliveries in the Department Oxytocin drip was also usually continued after delivery of the ch ld until the placenta had been expelled During this period the rate of infusion was usually increased Intranasal administra tion was usually terminated before the child was delivered For the final anæsthesia chloroform was used The total amount of blood lost at delivery is given in Table X

The amounts of oxytocin used in the two groups are given in Table XI The total amount given by intravenous drip was on the average 6 7 I U The corresponding amount for intranasal applica tion was 99 I U thus about 15 times as much The amount given intranasally could probably be reduced with greater experience of the method

Four of the mothers received oxytocin intravenously *and* intra nasally These 4 cases date back to the term when we had had l t le experiences with the intranasal application In one case an

Table XI *Total Doses of Oxytocin and Average Dose per Patient*

Oxytocin Intravenous	Oxytocin Intravenous	Oxytocin Intranasal	Oxytocin Intravenous +	Oxytocin Intranasal	Oxytocin Intranasal
– 5 I U	48	12	–	–	– 10 I U
5 1– 7 5	8	12		2	11– 20
7 6–10	13	16	1	–	21– 40
11 –15	7	28	–	1	41–100
16 –20	2	15	2	–	101–200
> 20	6	10	–	1	201–500
		3			> 500
Amount not noted	48	–	1	–	
Average dose	6 7 I U	9 9 I U			

oxytocin-drip was given first without any effect, and the following day oxytocin was given intranasally with good effect In another case the patient received 3 courses of treatment with oxytocin intranasally on 3 consecutive days with a moderate effect The fourth day oxytocin was given by intravenous drip with a good effect In the third case oxytocin given intranasally had a moderately good effect The following day oxytocin by intravenous drip was given again with only a moderate effect, but the patient was delivered after a total amount of 18 I U intravenously In the fourth case the patient received oxytocin intranasally without any effect The following days she received oxytocin infusion, likewise without effect The fourth day oxytocin was given intranasally again, this time with a good effect

Discussion

It is clear from the results given in Table II that the effect of oxytocin given intranasally was almost as good as that obtained when the hormone was given by the intravenous route The difference in the effect can be explained, at least to a certain extent, by the differences in the composition of the series It is clear from Table V that in the group treated with oxytocin intravenously there were a larger number of cases in which the mem

branes had ruptured (82 per cent against 65 per cent) with the presenting part of the fœtus below the spinal plane (20 per cent against 10 per cent) and in weak labour (64 per cent against 55 per cent), when the treatment was started All these factors would favour a better response to the hormone in the drip series

An increased number of complications might have been expected with the intranasal administration, particularly overdosage, uterine tetany and fœtal asphyxia The frequency of such complications was, however, if anything, lower than with intravenous administration Fœtal asphyxia was equally common in both group, although the group that received oxytocin by intravenous drip included 2 cases of uterine tetany (Table IX), 1 case of premature separation of the placenta, and 5 cases of fœtal death, in which it was not possible to exclude the oxytocin drip as a cause of the fatal outcome No such cases occurred in the group that received oxytocin intranasally In this group two of the women were delivered by Cæsarean section the indications (one case of placenta prævia and one of brow presentation in a primigravida) for both operations had nothing to do with the intranasal administration of the hormone In both cases it might have been argued that oxytocin was contraindicated but it was nevertheless used to try to induce labour

The loss of blood during and after parturition appeared to be somewhat greater in the group that had received oxytocin intranasally In 4 of the cases belonging to this group more than 600 ml were lost In one of them (a 24 year old primigravida child 4,080 g) the bleeding was due to *post partum* atony of the uterus, in one case the cervix lacerated (31 year old primigravida with twins 1 850 g and 2 840 g) and in the other two cases the massive bleeding was due to retention of pieces of placenta It is questionable whether this can be ascribed to the therapy

The indications for oxytocin intranasally appear to be the same as for oxytocin by intravenous drip The contraindications are also the same Oxytocin cannot be applied intranasally in cases where the patient cannot cooperate as in serious toxæmia and when the absorption from the nasal mucosa is impaired as during a common cold Otherwise the intranasal method can replace intravenous infusion Intranasal application is simple and practical

and it does not inconvenience the patient at all, it makes no extra care of the patient necessary, and the patient can be up and about

The solution used for the intranasal administration was supplied by AB Ferring Malmo, Sweden, under the name of *Partocon LN*

SUMMARY

Intranasal administration of a solution containing 100 I U oxytocin per ml and given in a dose of 5–40 I U to induce or stimulate labour at term was found to have a rapid and reliable effect A series of 96 women treated with oxytocin intranasally in these doses is compared with a series of 132 women treated by intravenous infusion The results of the comparison are given below

1 The effect of the intranasal administration is as good as that obtained by intravenous drip
2 In the series studied complications were equally common in both but were less severe in the group that received the hormone by the intranasal route In the group that received the hormone by intravenous drip, 5 children were lost during labour or within a few hours of delivery, while no fœtal deaths occurred in the group that received oxytocin intranasally
3 Since application intranasally has considerable practical advantages and inconveniences the patient much less, this route appears to be preferable With but few exceptions this method of application can completely replace intravenous drip

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INCIDENCE OF PSEUDOMONAS ÆRUGINOSA AND OTHER GRAM-NEGATIVE RODS IN NEWBORN INFANTS

BY

HELGA LAURSEN

It appears that the administration of a humidified air-oxygen mixture in the treatment of premature infants and infants with respiratory impairment is attended with certain hazards, including hospital-acquired infections The object of this investigation was to study the incidence of such infections

The use of humidifying equipment apparantly gives rise to infection by Gram-negative rods occasionally leading to severe, or even fatal, septic conditions Thus in 1955, Hoffmann and Finberg published a study on infections by Pseudomonas æruginosa (Bacillus pyocyaneus), which occurred in 13 infants within a period of 12 months All these infants had been admitted to a premature nursery with a high-humidity environment Pseudomonas septicæmia developed in three of these 13 infants The portals of entry of the infections were mainly the umbilicus, skin and conjunctivæ Thus, umbilical infection was encountered in seven, skin eruptions in four and conjunctivitis in three of the infants Cultures of material from the infections yielded Ps æruginosa in all 13 cases Five of the infants died, probably from the infection, although prompt treatment with Polymix B was instituted

Neter and Weintraub, also in 1955, presented a series of 143 infants from a premature nursery who had been studied for Ps æruginosa colonisation Swabs were obtained from the naso-

harynx, pharynx and skin, and also from fæces, Ps æruginosa was ultured from the nasopharynx in 27 per cent, and from the pharynx in 40 per cent of the cases The majority of these infants did not reveal any clinical infections by Ps æruginosa Only a few patients had pustular skin lesions, diarrhœa or bronchopneumonia which might be referable to this micro organism but five had generalised Ps æruginosa infections, and four died

In 1961, Burns and Rhodes emphasised the danger involved in ocular Ps æruginosa infections in premature infants they had collected nine cases, including four in whom fatal septicæmia developed

In systematic studies of humidifying equipment, Macpherson (1958) found gross contamination of humidifiers cocks and tubing, mainly by Gram negative rods, and stressed the risk of infecting patients who are given oxygen treatment by means of such equipment The distilled water used in the humidifiers was also grossly contaminated Because of the contamination and the difficulty involved in cleansing the equipment, these pathogenic rods are transmitted directly to the patients through the nasal catheters Similar conditions were revealed by Dons, Eriksen and Jorgensen (1959) in a Ps æruginosa epidemic in the Department of Thoracic Surgery at Rigshospitalet, Copenhagen - In both of these studies, the following procedures were strongly recommended (a) Only absolutely sterile water should be used (b) the humidifying units should be meticulously cleaned and (c) water should be poured into the humidifiers only immediately before use

These procedures may be directly applied to oxygen treatment of infants whether this is given in incubators or by oxifiers The need for this is confirmed by the report published by Sever in 1959 In his study of humidifying devices and the distilled water used in these he found gross contamination by pathogenic micro organisms especially Gram negative rods After the institution of certain changes in the procedures and in the cleansing of the equipment and by the use of absolutely sterile water the degree of bacterial contamination was significantly reduced

It is obvious that such contamination is of great clinical importance and it has gradually been realised that micro-organisms

which are generally considered to be non pathogenic may, in certain circumstances, cause severe, or even fatal, infections in debilitated patients Thus, Shermann *et al* (1960) reported two cases of fatal pulmonary infection by Alcaligenes fæcalis in premature infants who had both received oxygen treatment Wilson *et al* (1961) studied the utensils in a newborn nursery in which a fatal Ps æruginosa infection had occurred in a premature infant, filters mounted on the water cocks of the wash hand basins were found to be grossly contaminated by this micro-organism Foley *et al* (1961) described six cases of fatal septicæmia occurring in a newborn nursery within 3 months, four of these cases were due to a Gram-negative rod belonging to the genus of Achromobacter The same organism was demonstrated in the water in the humidifying pan in an incubator and in water which was used for bathing the eyes of the infants

Cabrera and Davis (1961) described an epidemic due to Flavobacterium meningosepticum, extending over 3 months Infections developed in 14 infants, 10 died, three survived with defects (hydrocephalus), and one recovered apparently without consequent harm The same micro-organism was isolated from nasal swabs from another 30 infants, whereas the nursing staff was not found to be infected Studies of the hospital equipment revealed a defective water trap which was grossly contaminated

In spite of the fact that a relatively large number of severe infections caused by various Gram-negative rods have gradually been reported, the aforementioned study by Neter and Weintraub (1955) seems to be the only survey in the literature on the incidence of nasal carriage of Gram negative rods in infants treated with oxygen in the neonatal period

Personal Investigations

In a series of nasal swabs secured in infants, mainly with a view to studying colonisation with Staphylococcus aureus, it was revealed that a strikingly large number of infants were nasal carriers of Ps æruginosa and other Gram negative rods These infants were selected for a closer study

The investigations reported in this paper were performed in the Maternity Clinic B, of Rigshospitalet, Copenhagen, during the period from Jan 1, 1958, to Aug 31, 1960, and comprised nasal swabs from mothers and infants taken during the hospital stay, which ranged from a few days up to 2–3 weeks, but usually lasted 8–10 days Swabs were taken routinely twice a week In addition swabs were occasionally obtained just before discharge and, in some of the infants, umbilical swabs were secured on the day the stump of the cord separated

The series consists of a total of 5,774 registrations most of which comprise a mother and her baby, but there were also some mothers without babie, and a few babies without mothers Birth of twins and triplets occurred in 76 and 2 cases, respectively Nasal swabs were obtained in a total of 5,109 infants during the period under consideration

All patients were swabbed with sterile cotton in both nostrils and the specimens were seeded on blood agar plates as quickly as possible, i e within one or two hours after incubation at 37° C the cultures were read at 24 and 48 hours

The pathogenic micro organisms recovered from the nasal swabs are listed in Table I

Table I *Incidence of Pathogenic Micro-organisms in Nasal Swabs from 5 109 Infants*

	No of Cases	
Ps æruginosa	103	
Other Gram negative rods	296	399 infants = 7 6 %
Staph aureus	2 267	44 4 %
Pneumococci	17	
Hæmolytic streptococci	7	
Yeasts	11	

Ps æruginosa and Proteus were easily identifiable because of their characteristic mode of growth on the primary plates The group classified as other Gram negative rods (including Proteus) was studied for lactose fermentation and most of the strains recovered were tested for sensitivity to various antibiotics In

addition to the pathogenic micro-organisms shown in Table I, various samples revealed growth of Staph. albus and diphtheroid rods, but these organisms were excluded from the survey as their presence was interpreted as a sign of a 'normal nasal flora'.

Ps. æruginosa and other Gram-negative rods were present in 388 infants, i.e. in 7.6 per cent of the 5,109 infants studied. Nasal carriage of both types of bacteria was revealed in 11 cases. As compared with the number of staphylococcal carriers, the 7.6 per cent carrier incidence is not at all alarming, but a division of the series into infants placed in the premature nursery and those placed elsewhere gives a completely different picture (Table II).

Table II *Distribution of Pathogenic Micro-organisms in 5,109 Infants Placed in and outside the Nursery*

	In Nursery No.	In Nursery %	Not in Nursery No.	Not in Nursery %	Total No.	Total %*
Infants in whom nasal swabs were obtained	963	18.8	4,146	81.2	5,109	
Ps. æruginosa	91	9.4	12	<0.3	103	2.0
Other Gram-negative rods	204	21.3	92	2.2	296	5.8
Staph. aureus	372	38.6	1,895	45.8	2,267	44.4
Pneumococci	4		13		17	
Hæmolytic streptococci	1		6		7	
Yeasts	2		9		11	

Both before and during the period of investigation the clinic employed the so-called 'rooming-in' system, i.e. the mother and baby are placed in the same room. Only when required by special circumstances – in cases of prematurity or if some specific treatment or closer observations is considered to be necessary – are the infants placed *in the nursery*, which consists of two adjoining rooms. In one of these rooms there are incubators and a few cradles, while the other is furnished with cradles to which an oxifier can be attached, and a bed which can be provided with an oxygen tent and Alevaire® equipment. If infection is suspected, the infants concerned is, as far as possible, isolated in some other room in the clinic.

It is seen from Table II that the occurrence of Staph. aureus, pneumococci, hæmolytic streptococci and yeasts does not present

any special problem as far as the nurserv infants are concerned The incidence of staphylococcal carriage is even slightly lower than in the other group of infants, which is surprising in view of the numerous reports warning against the increased risk of staphylococcal cross infection when many infants are placed together in the same room None of the infants whose nasal swabs revealed pneumococci, hæmolytic streptococci or yeasts presented signs of clinical infection

Table III *The Distribution of Ps æruginosa and Other Gram negative Rods in Infants Nursed inside and outside the Nursery The Tabulation Comprises 399 Bacterial Strains Obtained from 388 Nasal Swabs The Percentages are Calculated from the Number of Infants with Positive Findings*

	In Nursery No		Not in Nursery No	%
Ps æruginosa	91	23 5	12	3 1
Other Gram negative rods	204	52 6	92	23 7
Total	295	70 0	104	26 8

Table III shows the distribution of Ps æruginosa and other Gram negative rods in infants placed in and outside the nursery Of the 388 infants in whom nasal swabs revealed growth of these organisms, 76 per cent had been admitted to the nursery

Finally the infants placed in the nursery were divided into two groups, *viz* one treated with oxygen and another in which no oxygen treatment was given (Table IV)

Table IV *Inciden e of Ps æruginosa and Other Gram negative Rods among Nursery Infants who Were and Were Not Given Oxygen Treatment*

	Incubator and Oxygen No		Oxifier	N Oxygen Therapy	No Information as to Oxygen Therapy
Ps æruginosa	80	87 9	2	9	0
Other Gram-negative rods	163	81 9	10	26	5
Total	243	83 9	12	35	5

Among the infants from whom Ps æruginosa was recovered 90 1 per cent had received oxygen treatment almost invariably in an incubator Among the 199 infants who were nasal carriers

of other Gram-negative rods, and for whom it was expressly stated whether or not they had received oxygen, this therapy had been employed in 86 9 per cent, in most cases given in an incubator

A review of the hospital records showed that Alevaire® treatment had been employed in 31 of the 388 infants because of respiratory insufficiency Among these, Ps æruginosa was recovered in 16 and other Gram negative rods in 18 (both types of bacteria were cultured from the same nasal swab in three cases) The ratio of Ps æruginosa to other Gram-negative rods was strikingly high, *viz* approximatively 1 1, as compared with about 1 3 in the entire series

In view of these findings, the utensils in the nursery were subjected to bacteriological studies during two periods in 1959 and 1960 Swabs from Alevaire® equipment yielded some colonies of Ps æruginosa, and numerous colonies were obtained from samples of water in the humidifiers and from the plastic outlet tubing A closer study of an incubator revealed growth of numerous colonies in material obtained from a 'clean,' moist face cloth which had been placed in the head end of the incubator in order to give a suitable humidity This incubator had been used for 48 hours (the face cloth had, however, been changed the same morning), a nasal swab from the infant who had been in the incubator yielded numerous lactose-fermenting Gram negative rods, and an umbilical swab showed growth of yeast cells Nasal swabs from three infants who had been treated with an oxifier on the same day produced numerous colonies of Ps æruginosa or other Gram negative rods It was shown that the cover of a hot water bottle placed in the cradle occupied by one of these infants harboured numerous Gram negative rods A sample of distilled water in a plastic storage bottle closed with a screw cap yielded some colonies of Ps æruginosa and other Gram negative rods

It appears from Table II that among the infants who had not been admitted to the nursery, 12 harboured Ps æruginosa and 92 other Gram-negative rods The hospital records of these 104 infants were reviewed in order to disclose if there were any contributory pathogenic factors or signs of pathological conditions (Table V)

Table V Pertinent Data from the Hospital Records of 104 Nasal Carriers Not Admitted to the Nursery

	No of Cases
Normal conditions	18
Born before arrival in hospital	4
Difficult or protracted labour forceps delivery, rupture of membranes more than 24 hours before delivery	16
Cæsarean section	4
Mother infected at time of delivery	7
Renal disease in mother	11
Oxygen and suction employed at delivery	2
Large infant ($>$ 4 000 g)	9
Prematurity ($<$ 3 000 g)	33
Post maturity (with low birth weight)	1
Icterus neonatorum	37
Tendency to regurgitation	3
Harelip cleft palate	1
Diarrhœa	1
Twin A (twin B stillborn macerated)	1

It will be seen that many obstetrical complications and some post natal anomalies were recorded Only 18 deliveries were perfectly normal this figure is surprisingly low in view of the clientele of the clinic Several pathogenic factors were observed in some of the cases

Of the 399 bacterial strains encountered 353 were studied for lactose fermentation and sensitivity to various antibiotics and sulphonamides Their ability to ferment lactose was tested by seeding on bromthymol blue lactose agar plates, and their sensitivity to sulphathiazole streptomycin terramycin, chloromycetin and penicillin was determined by K A Jensen s filter paper disc method as described by Moltke and Eriksen (1957) All strains showing a zone of inhibition of less than 25 mm were classified as resistant All the strains were resistant to ordinary doses of penicillin (i e the disc was imbibed with 0 05 ml of a penicillin solution of 50 Oxford units/ml) Accordingly the penicillin sensitivity refers to large" doses of penicillin (i e, the

disc was imbibed with 0 05 ml of a penicillin solution of 100,000 Oxford units/ml)

Ps æruginosa could be identified immediately because of its production of pigment, which gives rise to a characteristic greenish grey colour of the colonies This micro-organism is also characterised by its pattern of resistance, all strains being either completely resistant or only weakly sensitive to streptomycin and/or sulphathiazole, but otherwise resistant

As previously pointed out, 103 strains of Ps æruginosa were encountered Proteus is readily identifiable because of its motility and characteristic smell, five unspecified strains of this organism were isolated Of the remaining 291 bacterial strains, 245 were subjected to a closer study, of these, 201 were found to be lactose-fermenting and 44 non lactose-fermenting

The pattern of resistance was as shown in Table VI

As appears from this table, the majority of the bacterial strains did not reveal any great resistance to the antibiotics studied This is in agreement with the fact that the standard treatment used in the clinic consists in administration of penicillin, possibly supplemented by streptomycin, while broad-spectrum antibiotics are used as little as possible

The clinical infections caused by micro organisms other than Staph aureus which occurred among the infants during the same period, and which were confirmed by bacteriological studies, are shown in Table VII

Finally, as a manifestation of more extensive colonisation, concurrent growth of Ps æruginosa was obtained from nasal and umbilical swabs in two cases and of yeast cells from nasal and umbilical swabs in one case In one case of conjunctivitis caused by lactose fermenting, Gram-negative rods, growth of this micro organism and Staph aureus was obtained from an umbilical swab taken at the same time During the period of investigation ocular swabs were secured in 126 cases, this gives a frequency of infections caused by Ps æruginosa and other Gram negative rods of 6 3 per cent, but this percentage should be evaluated with some reserve in view of the relatively small figures

When these infections were related to whether or not the infant had been admitted to the nursery, it was seen that only two

Table VI *Pattern of Resistance of 353 Bacterial Strains*

	No. of Strains
A. *Ps æruginosa*	
Completely resistant	77
Weakly sensitive to sulphathiazole otherwise resistant	19
Weakly sensitive to streptomycin	2
Weakly sensitive to sulphathiazole and streptomycin	5
Total	103

B. *Other Gram negative rods*	Lactose-fermenting	Non-lactose fermenting	Proteus
Sensitive	175	28	
Resistant to			
Sulphathiazole	7	8	
Streptomycin	1	2	
Terramycin			3
Chloromycetin		4	
Sulphathiazole and penicillin	4		
Streptomycin and penicillin	2		
Sulphathiazole and terramycin			2
Sulphathiazole terramycin and penicillin	3		
Sulphathiazole and chloromycetin		1	
Chloromycetin and penicillin	6		
Sulphathiazole streptomycin chloromycetin and penicillin		1	
Terramycin chloromycetin and penicillin	1		
Completely resistant	2		
Total	201	44	4

had been in the same room as the mother while the remaining infants had been in the nursery The first two infants had conjunctivitis caused by lactose fermenting rods and enterococci, respectively The two severe generalised infections by Gram negative rods (Escherichia coli meningitis and Ps æruginosa septicæmia) must be excluded because both infants were infected before they were admitted to the nursery The E coli meningitis occurred in an infant after a very difficult delivery On admission

Table VII *Non staphylococcal Clinical Infections Occurring in the Maternity Clinic during the Period of Investigation*

Type of Infection	Causative Agent	No of Cases
Meningitis	E coli[1]	1
Septicæmia	Ps æruginosa	1
Generalised moniliasis (stomatitis and skin affection)		1
Conjunctivitis		
	Lactose ferm Gram neg rods	6
	Ps æruginosa	2
	Enterococci	1
Skin affections		
Pustular lesions	Lactose-ferm Gram neg rods	1
Abscess of the heel	Lactose ferm Gram neg rods	1
Napkin area dermatitis	Yeasts	4
Ulcers	Hæmolytic streptococci	1
Ulcers	Lactose-ferm Gram neg rods and enterococci	1
Umbilical infection	Ps æruginosa	1
	Total	21

[1] Identified by Dr H Lautrop and typed by Dr P Ørskov, of the State Serum Institute, Copenhagen

the mother was found to be infected by the same type of coli form organism as was later cultured from the spinal fluid of the infant which survived The Ps æruginosa septicæmia occurred in an infant who had been transferred to the clinic from another hospital in very poor condition, death occurred shortly afterwards Ps æruginosa was cultured from the pericardial fluid, both lungs, liver, spleen, intestinal tract and peritoneal fluid Nasal swabs revealed abundant growth of Ps æruginosa and a few colonies of Staph aureus, which belonged to phage type 187 and was sensitive to all the antibiotics studied As umbilical swabs showed growth of numerous colonies of Ps æruginosa, it may be assumed that the portal of entry of the infection had been the umbilicus

Neonatal meningitis and septicæmia are rare conditions which often escape recognition *ante mortem* because of the vague symptoms produced, but these severe infections are frequently caused

by Ps æruginosa and other Gram negative rods During recent years, E coli meningitis has increased in frequency as compared with meningeal infections due to streptococci and pneumococci, which have become extremely rare in this age group In 1957, Watson reported 45 cases of purulent meningitis with a mortality of 64 per cent In 73 per cent of the cases the causative agent was Gram negative rods (E coli, 14 Ps æruginosa, 2, Ærobacter ærogenes, 1, and other Gram negative rods 16 cases)

In 1958, Mohsen Ziai and Haggarty published a survey on 83 cases of neonatal menigitis occurring within a 25 year period, 62 of the patients died in the acute phase of the disease Bacteriological studies revealed E coli, 25 Ps æruginosa, 4 A ærogenes, 3 and other Gram negative rods, 7 cases The infants subjected to autopsy showed neonatal meningitis in 4 8 per cent of the cases

Nyhan and Fousek, likewise in 1958, published a similar survey on neonatal septicæmia, it comprised 106 infants seen during a 25 year period Among 65 positive cultures of blood (taken *ante mortem*) E coli was present in 20 and Ps æruginosa in 4 cases The mortality rate was 72 per cent Also in this series, septicæmia caused by Gram negative rods was predominant during the later years of the study period The most frequent con comitant finding was meningitis the spinal fluid revealed E coli in nine case and Ps æruginosa in three Skin affections were demonstrated to be due to E coli in one and to Ps æruginosa in three cases Positive umbilical swabs showed E coli in one and Ps æruginosa in three cases nasopharyngeal swabs revealed Ps æruginosa in one case and ocular swabs yielded Ps æruginosa in one case

As compared with these reports the frequency of infections in the present series is very low but the studies are not directly comparable because the publications just mentioned originated from pædiatric departments with sick children while the present series is from a maternity clinic in which these conditions were not subjected to specific investigations and in which infants with signs of severe infection are promptly transferred to other depart ments for further examination and treatment

Conclusions

The occurrence of Ps æruginosa and other Gram negative rods in newborn infants who have been in the clinic nursery is apparently related to the humidified atmosphere, the air being contaminated with these micro organisms It is undoubtedly very difficult to avoid this contamination, since these micro-organisms may be present in the intestinal tract and can multiply in water and at lower temperatures than most other pathogenic bacteria It is also difficult to clean the humidifying equipment adequately It is not easy to determine the importance of the colonisation of the nasal mucosa, but as the infants are often premature and weak, such a colonisation constitutes a problem which deserves attention, just as does colonisation by Staph aureus

As regards the infants who had not been admitted to the nursery and nevertheless harboured pathogenic Gram negative rods in the nasal mucosa, the review of the hospital records revealed that relatively few of the infants (18 out of 104) were in perfect health after a normal delivery, it is conceivable that many of the remaining infants were infected during delivery In addition, the "sterile" water which is used both for infants and mothers, may easily contain these organisms and thus constitute an potential source of infection Bacteria were demonstrated in the "sterile" water in the nursery, but the importance of this source of infection has not yet been subjected to a closer study

It appears from the present study that the risk of serious infections among the infants is relatively slight, although it must constantly be borne in mind Some neonatal deaths of unknown cause might prove to be due to infections if autopsy in such cases was supplemented by bacteriological studies

It appears to be imperative that all humidifying equipment be meticulously cleaned immediately after use, and that only absolutely sterile water be used in such equipment of for any other purposes in a maternity clinic Finally, it must be borne in mind that infants infected by these bacteria may exhibit only very vague and atypical symptoms, even in the presence of a very severe infection

SUMMARY

Bacteriological studies on the incidence of nasal carriage of Ps æruginosa and other Gram negative rods in newborn infants from a maternity clinic are presented The investigation extended over a period of 32 months These micro-organisms were revealed in 7 6 per cent of 5,109 infants The majority of the babies had been treated with humidified oxygen Seventy six per cent of the infants harbouring Ps æruginosa and other Gram negative rods had been admitted to the nursery, and 88 per cent of the nursery infants had been given oxygen treatment The utensils used in the nursery, especially the humidifying equipment and the sterile" water, were found to be contaminated by these bacteria Clinical infections by the organisms concerned were rare, but occurred most frequently in infants who had been admitted to the nursery

It is essential that all humidifying equipment be meticulously cleaned, and that only absolutely sterile water be used in such equipment or for any other purposes in a maternity clinic

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THE CAUSES OF PERINATAL DEATH

BY

L. LINDGREN, P. NORMANN AND L. VIBERG

The literature on perinatal death is extensive. The detailed causes are numerous, and since the case material is derived from populations of varying composition, the relative importance of individual causes is variable. Results are therefore not truly comparable.

In Sweden the factors involved in perinatal death have been investigated by Thoren (1948), Simon (1955), Strom (1953) and Kjessler (1955). At the Congress of the Northern Obstetricians and Gynæcologists held in Helsingfors, Finland, in 1960, perinatal mortality was one of the principle subjects for discussion (Kaern, Ahvenainen).

Although complications of pregnancy and labour are often responsible for perinatal death the underlying cause of death cannot be detected in a large number of cases. In many instances several factors are involved.

From a pathologico-anatomical point of view the causes of perinatal death can be divided into the following three groups: (i) severe congenital malformations of the fœtus, (ii) rupture of the tentorium, (iii) fœtal asphyxia.

Asphyxia may be caused by conditions such as complications resulting in obstruction of the umbilical cord, premature separation of the placenta, placenta prævia or indirectly by toxæmia of pregnancy, uterine inertia, breech presentation and multiple pregnancy. Those cases in which the underlying cause cannot be detected, are commonly associated with prematurity.

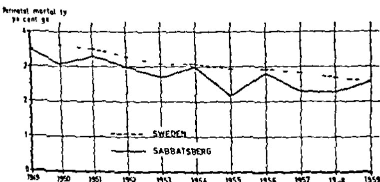


Fig 1

Perinatal mortality depends on the number and severity of the predisposing factors

In order to form an idea of the ætiological importance of the various factors involved in perinatal death, a series of cases col lected from the Department of Obstetrics and Gynæcology of the Sabbatsbergs Sjukhus in Stockholm, was investigated

Present Series

The case material comprised 23,836 infants from 23,372 preg nancies who were born in this Department in the years 1949–1959 A total of 647 infants were stillborn or died within 7 days of birth the perinatal mortality being 2 72 per cent (Tables I–III) A *post mortem* examination was performed in all cases There was practically no difference between the number of child ren born to primigravidæ and multigravidæ respectively being 11 948 in the former and 11 888 in the latter group The perinatal mortality rate in these two groups was 3 10 per cent and 2 33 per cent respectively

Of the 23 836 infants in this series 1 087 (4 56 per cent) were born prematurely (birth weight $\leqq$ 2 500 g) Of these 317 (29 2 per cent) died perinatally Almost one half (49 0 per cent) of all infants who died perinatally were premature

Intra uterine death before the onset of labour occurred in 220 (34 0 per cent) of the 647 cases of perinatal death

Table I *Number of Dead Infants Born to Primigravidæ and Multigravidæ*

	Birth Weight ≲ 2 500 g				Birth Weight > 2 500 g				Total			
	Prior to Labour	During Labour and After Delivery		Total No of Cases	Prior to Labour	During Labour and After Delivery		Total No of Cases	Prior to Labour	During Labour and After Delivery		Total No of Cases
		Rupture of Tentorium	Fœtal Asphyxia			Rupture of Tentorium	Fœtal Asphyxia			Rupture of Tentorium	Fœtal Asphyxia	
Severe malformation of the fœtus	11	8	25	44	14	2	36	52	25	10	61	96
Breech presentations	13	10	28	51	4	13	16	33	17	23	44	84
Toxæmia of pregnancy	22	4	20	46	7	7	8	22	29	11	28	68
Premature separation of the placenta	18	10	20	48	8	0	4	12	26	10	24	60
Primary inertia	0	0	4	4	2	19	33	54	2	19	37	58
Secondary inertia	0	0	2	2	2	2	3	7	2	2	5	9
Twins and triplets	11	3	26	40	0	2	7	9	11	5	33	49
Abnormal presentation	4	3	10	17	7	5	11	23	11	8	21	40
Complications involving the umbilical cord	4	0	1	5	8	0	13	21	12	0	14	26
Disproportion	1	0	0	1	1	8	9	18	2	8	9	19
Placenta prævia	0	1	9	10	0	0	3	3	0	1	12	13
Perinatal death from unknown cause Number of dead infants in the absence of complications	43	11	58	112	64	30	41	135	107	41	99	247
Total of dead infants	110	41	166	317	110	71	149	330	220	112	315	647

Obstetric Complications

The incidence of complications of pregnancy and labour was 17 2 per cent, representing 4,110 infants Of these 400 (9 7 per cent) died perinatally Thus, more than three fifth (61 8 per cent) of the perinatal deaths occurred in cases in which pregnancy or labour was complicated

The incidence of perinatal death in multigravidæ whose pregnancy or labour was complicated, was higher than in the corresponding group of primigravidæ, being 12 4 and 8 5 per cent respectively ($P < 0\ 001$)

The incidence of obstetric complications in primigravidæ was about twice as high as that found in multigravidæ, being 22 3 per cent and 12 2 per cent respectively ($P < 0\ 001$) In the former group uterine inertia and toxæmia of pregnancy were the chief complications and these accounted to a large extent for the larger number of perinatal deaths

On the other hand, the incidence of multiple pregnancy, placenta prævia and complications involving the umbilical cord (prolapse of the cord in cephalic presentation, true knots, and entanglements) was higher in multigravidæ

Table IV shows the perinatal mortality rates associated with the different complications The most serious complications were congenital malformations of the fœtus, premature separation of the placenta, and complications involving the umbilical cord Severe congenital malformations of the fœtus breech presentation toxæmia of pregnancy uterine inertia and premature separation of the placenta played the most important part in perinatal mortality It is interesting to note the high incidence of fœtal asphyxia in the cases in which no obstetric complication could be detected (Table I)

Severe Congenital Malformations of the Fœtus

Severe congenital malformations of the fœtus (anencephalus hydrocephalu abnormalities of the cardio vascular system mongolism etc) were found in 0 6 per cent of the 23 836 infants in this series and accounted for 14 8 per cent (96 out of 647

Table II *Number of Dead Infants Born to Primigravidæ*

	Birth Weight ≤ 2 500 g				Birth Weight > 2 500 g							
	Prior to Labour	During Labour and After Delivery		Total No of Cases	Prior to Labour	During Labour *and* After Delivery		Total No of Cases	Prior to Labour	During Labour *and* After Delivery		Total No of Cases
		Rupture of Tentorium	Fœtal Asphyxia			Rupture of Tentorium	Fœtal Asphyxia			Rupture of Tentorium	Fœtal Asphyxia	
Severe malformation of the fœtus	7	1	9	17	6	2	18	26	13	3	27	43
Breech presentations	8	6	14	28	0	12	13	25	8	18	27	53
Toxæmia of pregnancy	14	3	14	31	6	7	6	19	20	10	20	50
Premature separation of the placenta	11	8	11	30	2	0	2	4	13	8	13	34
Primary inertia	0	0	2	2	2	18	30	50	2	18	32	52
Secondary inertia	0	0	1	1	2	2	3	7	2	2	4	8
Twins and triplets	3	2	12	17	0	0	2	2	3	2	14	19
Abnormal presentation	0	1	6	7	5	5	4	14	5	6	10	21
Complications involving the umbilical cord	0	0	1	1	3	0	5	8	3	0	6	9
Disproportion	1	0	0	1	0	6	7	13	1	6	7	14
Placenta prævia	0	1	2	3	0	0	2	2	0	1	4	5
Perinatal death from unknown cause Number of dead infants in the absence of complications	16	6	33	55	33	21	24	78	49	27	57	133
Total of dead infants	50	26	85	161	55	56	98	209	105	82	183	370

cases) of the perinatal deaths There was no appreciable difference in the incidence of congenital malformations in infants born to primigravidæ and multigravidæ The mortality rate in these malformed infants in the two groups was also similar

Rupture of the Tentorium

Rupture of the tentorium occurred in 112 (17 3 per cent) of the 647 cases of perinatal death (Table I) The incidence was higher in full term infants than in premature infants being 21 5 per cent and 12 9 per cent respectively (0 01 > P > 0 001)

In primigravidæ (Table II) rupture of the tentorium was present in 22 6 per cent (82 out of 370 cases) of the dead infants and in multigravidæ (Table III) in 10 7 per cent (30 out of 277 cases), the difference being statistically significant (P < 0 001) In 41 cases no cause for the lesion other than the strain involved in normal delivery could be detected (Table I)

Rupture of the tentorium occurred in 23 cases of breech presentation 19 cases of primary uterine inertia 8 cases of disproportion and 8 cases of abnormal presentation

Rupture of the tentorium was found in a remarkably large number of cases of toxæmia of pregnancy (11 cases) and premature separation of the placenta (10 cases) In the cases of uterine inertia breech presentation abnormal presentation and disproportion rupture of the tentorium was the immediate cause of *perinatal death* in 28 6 per cent the corresponding percentage in the other cases being 11 9 per cent The difference is statistically significant (P < 0 001)

Fœtal Asphyxia

Of the 647 cases of perinatal death asphyxia was the immediate cause of death in 449 (69 3 per cent) In 208 (32 1 per cent of the total of cases) of these the cause of asphyxia was unknown In 107 of these 208 cases the infant was stillborn and in 101 cases the infant was premature

Perinatal Death in Premature Infants Of the obstetric complications breech presentation (41 cases) was commonest in pre

Table II *Number of Dead Infants Born to Primigravidæ*

	Birth Weight ≦ 2 500 g				Birth Weight > 2 500 g							
	Prior to Labour	During Labour and After Delivery		Total No of Cases	Prior to Labour	During Labour and After Delivery		Total No of Cases	Prior to Labour	During Labour and After Delivery		Total No of Cases
		Rupture of Tentorium	Fœtal Asphyxia			Rupture of Tentorium	Fœtal Asphyxia			Rupture of Tentorium	Fœtal Asphyxia	
Severe malformation of the fœtus	7	1	9	17	6	2	18	26	13	3	27	43
Breech presentations	8	6	14	28	0	12	13	25	8	18	27	53
Toxæmia of pregnancy	14	3	14	31	6	7	6	19	20	10	20	50
Premature separation of the placenta	11	8	11	30	2	0	2	4	13	8	13	34
Primary inertia	0	0	2	2	2	18	30	50	2	18	32	52
Secondary inertia	0	0	1	1	2	2	3	7	2	2	4	8
Twins and triplets	3	2	12	17	0	0	2	2	3	2	14	19
Abnormal presentation	0	1	6	7	5	5	4	14	5	6	10	21
Complications involving the umbilical cord	0	0	1	1	3	0	5	8	3	0	6	9
Disproportion	1	0	0	1	0	6	7	13	1	6	7	14
Placenta prævia	0	1	2	3	0	0	2	2	0	1	4	5
Perinatal death from unknown cause Number of dead infants in the absence of complications	16	6	33	55	33	21	24	78	49	27	57	133
Total of dead infants	50	26	85	161	55	56	98	209	105	82	183	370

Table IV *Perinatal Mortality Rate and Complications in Primigravidæ and Multigravidæ*

	Primigravidæ		Multigravidæ		Total percentages	
	Incidence	Perinatal Mortality %	Incidence	Perinatal Mortality	Incidence %	Perinatal Mortality %
Severe malformations in the fœtus	0 60	68 1	0 58	68 1	0 59	68 1
Breech deliveries	3 17	14 2	2 23	11 3	2 70	13 0
Toxæmia of pregnancy	3 67	10 9	1 19	14 2	2 43	11 7
Premature separation of placenta	0 51	45 9	0 45	59 3	0 48	52 2
Primary inertia	3 47	13 5	0 28	6 1	1 88	13 0
Secondary inertia	4 63	1 4	0 32	2 6	2 48	1 5
Twins and triplets	0 74	13 6	1 19	8 8	0 96	10 6
Abnormal presentations	3 62	4 8	3 52	4 5	3 57	4.7
Complications involving the umbilical cord	0 18	31 8	0 31	51 4	0 25	44.1
Disproportion	1 22	8 9	0 77	6 5	1 00	8 0
Placenta prævia	0 21	28 0	0 45	11 3	0 33	16 7
Perinatal death from unknown cause Number of dead infants in the absence of complications	77 72	1 50	87 85	1 02	82 76	1 25

mature infants who died of asphyxia, but in the majority of these cases this complication did not appear to be a contributing cause of fœtal death

The commonest complications were toxæmia of pregnancy (42 cases) premature separation of the placenta (38 cases) and multiple pregnancy (37 cases) The incidence of the latter condition was higher in multigravidæ whilst the incidence of the two first mentioned complications was higher in primigravidæ

Fœtal Death before the Commencement of Labour In 195 of the 647 cases of perinatal death asphyxia was the cause of the death of the fœtus prior to the commencement of labour In 107 (54 9 per cent) of these *post mortem* examination was impossible because of maceration of the fœtus In the remaining 88 cases the commonest complications were toxæmia of pregnancy (29 cases) and premature separation of the placenta (26 cases) This also held good if the cases were grouped according to parity

Table III *Number of Dead Infants Born to Multigravidæ*

	Birth Weight ≦ 2 500 g				Birth Weight > 2 500 g				Total			
	Prior to Labour	During Labour and After Delivery		Total No of Cases	Prior to Labour	During Labour and After Delivery		Total No of Cases	Prior to Labour	During Labour and After Delivery		Total No of Cases
		Rupture of Tentorium	Fœtal Asphyxia			Rupture of Tentorium	Fœtal Asphyxia			*Rupture of Tentorium*	*Fœtal Asphyxia*	
Severe *malformation* of the fœtus	4	7	16	27	8	0	18	26	12	7	34	53
Breech presentation	5	4	14	23	4	1	3	8	9	5	17	31
Toxæmia of pregnancy	8	1	6	15	1	0	2	3	9	1	8	18
Premature separation of the placenta	7	2	9	18	6	0	2	8	13	2	11	26
Primary inertia	0	0	2	2	0	1	3	4	0	1	5	6
Secondary inertia	0	0	1	1	0	0	0	0	0	0	1	1
Twins and triplets	8	1	14	23	0	2	5	7	8	3	19	30
Abnormal presentation	4	2	4	10	2	0	7	9	6	2	11	19
Complications involving the umbilical cord	4	0	0	4	5	0	8	13	9	0	8	17
Disproportion	0	0	0	0	1	2	2	5	1	2	2	5
Placenta prævia	0	0	7	7	0	0	1	1	0	0	8	8
Perinatal death from unknown cause Number of dead *infants in* the absence of complications	27	5	25	57	31	9	17	57	58	14	42	114
Total of dead infants	60	15	81	156	55	15	51	121	115	30	132	277

the country On dividing the cases into the 5 year groups 1949 to 1954 and 1955 to 1959 it was found that the decrease was due to a fall in the mortality rate during and after labour whilst the mortality rate prior to the commencement of labour remained unchanged (Table V) Thus, a decrease in the perinatal mortality rate during and after labour in cases of full term and complicated pregnancies accounted for the reduction of the over all perinatal mortality rate (Table VI)

Of the pathologico anatomical causes of death the perinatal mortality from rupture of the tentorium showed the greatest decrease (31 cases or 1 92 per cent out of 1 615 and 18 or 0 92 per cent out of 1,960 respectively, $0\,01 > P > 0\,001$) the corresponding figures for the perinatal mortality from asphyxia being 61 or 3 78 per cent out of 1,615 and 54 or 2 5 out of 1,960 ($P < 0\,05$)

Discussion

Evaluation of the various factors involved in perinatal mortality presents great difficulty for several reasons One reason is the varying composition of the cases published another reason is that it may be practically impossible to differentiate the immediate cause of perinatal death in cases in which several factors are involved If only clear cases i e cases in which a single cause of death is found, are considered, the case material represents selected cases At one stage in this investigation we sorted out such cases and analysed them but the findings did not in any way bias the conclusions drawn from the total of cases

In about two fifth of the cases of perinatal death pregnancy and labour were complicated About half of the *infants* who died perinatally were born prematurely With the exception of the group in which no cause of perinatal death other than debility of the fœtus was detected the principle causes of prematurity were toxæmia of pregnancy and premature separation of the placenta which is often associated with toxæmia of pregnancy This group included a large number of cases in which fœtal death of unknown cause occurred prior to the commencement of labour Kjessler (1955) and others have expressed the view that attempted

Table V *Perinatal Mortality Rate for the Years 1949–1959*

	1949–1954 %	1955–1959 %	1949–1959 %
Prior to labour	0 90	0 90	0 90
During labour and after delivery	2 14	1 54	1 82
Total	3 04 (10,041 infants)	2 44 (12,895 infants)	2 72 (23,836 infants)

Of the different complications the highest foetal mortality rate was associated with complications involving the umbilical cord These constituted 46 2 per cent of the perinatal deaths before the commencement of labour in this group, that of premature separation of the placenta and toxæmia of pregnancy being 43 3 and 12 6 per cent respectively In the group in which no cause of perinatal death was detected, the foetal mortality rate before the onset of labour was 43 3 per cent of all dead fœtuses in this group

Infant Mortality during and after Labour The highest mortality of infants who died of asphyxia during or after labour, was associated with breech presentation (44 cases), uterine inertia (42 cases), multiple pregnancy (33 cases), and toxæmia of pregnancy (28 cases) In the group of full-term infants uterine inertia (36 cases), breech presentation (16 cases) complications involving the umbilical cord (13 cases), abnormal presentations (11 cases) and disproportion (9 cases) were the commonest complications

Asphyxia not associated with any other complication accounting for perinatal death, was found in 41 full term infants Of these 41 infants, 12 born to multigravidæ and 7 born to primigravidæ, were more than two weeks post mature Thus, of the total of cases no cause of perinatal death other than the strain involved in normal delivery was found in 29 (4 5 per cent)

Comparison of the Perinatal Mortality Rate for Different Periods of Time

The perinatal mortality rate was found to have decreased in this series in the years 1949 to 1959 (Fig 1) as it has all over

criminal abortion accounted for intra uterine fœtal death in many of these cases Attempted criminal abortion and severe congenital malformations of the fœtus were the main causes of fœtal death prior to the commencement of labour in this series

Whilst the ætiology of toxæmia of pregnancy is not yet understood severe congenital malformations of the fœtus have been reported to be due to a viral infection of the mother early in pregnancy If this is the only underlying cause children of primigravidæ and multigravidæ should be equally affected However, in the present series the number of infants showing severe congenital malformations was slightly larger in the group of multigravidæ, probably because of the higher incidence of mongolism in this group

Rupture of the tentorium was found to occur mostly in cases of obstetric complications such as breech presentation uterine inertia abnormal presentation, and disproportion which may cause damage to the fœtal head Rupture of the tentorium also accounted to a large extent for the higher mortality rate during and after labour in infants born to primigravidæ The cases in this series in which the trauma caused by normal birth was the only cause of peri natal death, also formed a large group The relatively high incidence of rupture of the tentorium in the fœtus in cases of toxæmia of pregnancy and premature separation of the placenta is of interest because it indicates that damage to the fœtal head is not the only factor concerned in the causation of the condition

Asphyxia was the principle factor involved in perinatal death in this series This group included a relatively large number of full term infants who died of asphyxia during or after labour the majority being post mature This indicates that post maturity associated with insufficiency of the placenta is of major ætiological importance

The present investigation confirmed the observation that the over all perinatal mortality rate has decreased in recent years In this series this decrease was due to the low fœtal mortality rate during labour and the low mortality rate after delivery for infants born to mothers whose pregnancies had been complicated The improvement in the facilities for shortening labour probably resulted in an increasing number of infants saved

Table VI *Perinatal Mortality Rate and Birth Rate in Cases of Complicated Pregnancy and Labour and Normal Pregnancy and Labour in the Years 1949–1959*

	Birth Weight	1949–1954	1955–1959	1949–1959
Complicated pregnancy and labour	$\lesssim$ 2,500 g	38 9 (105 out of 270)	37 7 (100 out of 265)	38 3 (205 out of 535)
	$\gtrsim$ 2,500 g	6 7 (108 out of 1,615)	4 4 (87 out of 1,960)	5 5 (195 out of 3,575)
	Total percentages	11 3 (213 out of 1,885)	8 4 (187 out of 2,225)	9 7 (400 out of 4,110)
Normal pregnancy and labour	$\lesssim$ 2,500 g	19 2 (55 out of 287)	21 5 (57 out of 265)	20 3 (112 out of 552)
	$>$ 2 500 g	0 7 (58 out of 8,769)	0 7 (77 out of 10,405)	0 7 (135 out of 19,174)
	Total percentages	1 2 (113 out of 9,056)	1 3 (134 out of 10,670)	1 3 (247 out of 19,726)

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OVARIAN ARRHENOBLASTOMA

Case Report and Discussion of the Steroid Metabolism

BY

NILS LUNDGREN

Virilism of ovarian origin has been described in association with a number of less well differentiated conditions and tumours of the ovaries One form of such tumours is that for which Robert Meyer coined the name arrhenoblastoma because of its morphological similarity with the male gonads

This paper is concerned with a case of ovarian arrhenoblastoma observed for a long period during which the pattern of the urinary hormones was studied on various occasions

Report of case

A 28 year old healthy nullipara who had otherwise menstruated regularly was first seen in Sept 1953 because of 2 months amenorrhœa (L.M. 28/7) She thought that she was pregnant She had no molimina Gynæcological examination revealed nothing of interest and the uterus was of normal size Habitus and secondary sex-characters were feminine There were no signs of virilism

The *basal temperature curves* for the subsequent 4 months were monophasic and of medium height. *Rœntgenography* showed no abnormality of the sella turcica *Adrenalin test* normal reduction in the total number of eosinophils Curettage atrophic endometrium *Hormone analysis* (Febr 1954 after 7 months amenorrhœa) see Table 1 B M R minus 11 % Thyroid in a dose corresponding to thyroxin 0 2 mg daily was prescribed — Provocative treatment with ethinyl œstradiol and progesterone for 4 months produced no bleeding

This is also confirmed by the reduction of the number of cases in which rupture of the tentorium and asphyxia during and after labour were responsible for perinatal death

SUMMARY

The causes of perinatal death were investigated on the basis of the *post-mortem* findings in 647 cases of perinatal death These cases were collected from the Department of Obstetrics and Gynæcology of the Sabbatsbergs Sjukhus in Stockholm in the years 1949 to 1959 The total number of children born in this Department during that period was 23, 836 and the total of deliveries was 23,372

The factors concerned in the decrease of the perinatal mortality rate in Sweden during the past decade are discussed

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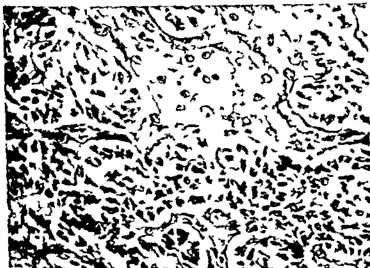


Fig 2 Same case as in Fig 1 A group of pale interstitial cells is seen in middle of upper margin and tubular formations in rest of section (× 350)

(Figs 1 and 2) showed a typical picture of arrhenoblastoma with mainly highly differentiated formations of the type seen in tubular adenoma but in some areas low differentiation (Dr Norden)

After the operation the patient was treated with roentgen irradiation of two right sided parametric fields (2,400 r to each) with the left ovary shielded

One month after the operation menstruation recurred spontaneously and has since occurred at regular intervals Judging from the basal temperature curve and endometrical biopsy the cycles were ovulatory Virilization (hypertrichosis male contour of pubic hair enlargement of clitoris and lowering of voice) disappeared within a year and the patient has since born two children one on August 31 1956 (last menstruation 17 11 55) and one on September 7 1959 (last menstruation 21 11 58)

The total neutral 17 KS were determined by the method of Jensen and Totterman (1952) The so-called D fraction (DF) was separated from the total neutral 17 KS by a differentiated hydrolysis and extraction technique (Jensen 1950) No attempts were made to fractionate the total neutral 17-KS further Judging from the results of the analysis DF consisted of dehydroepiandrosterone (DHEA) only but the possibility of the presence of minute amounts of androst 4-en 3 17-dione cannot be excluded

Two weeks after the operation the total neutral 17 KS level which was distinctly elevated immediately before operation fell considerably towards

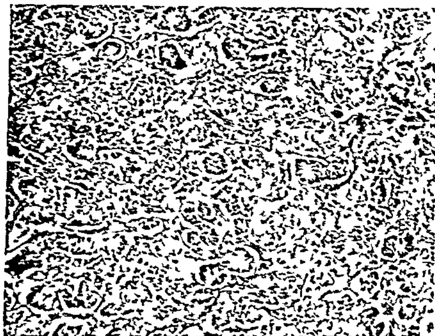


Fig 1 Ovarian arrhenoblastoma. Mainly highly differentiated formations of tubular adenoma type but low differentiation in some areas (v Giesen × 115)

Ten months after the onset of amenorrhœa hair began to appear on the upper lip but no other signs of virilization were seen The right ovary was slightly enlarged. – Six months later the right ovary had assumed the size of a hen's egg and virilization had progressed hairgrowth on the upper lip and limbs was now marked the superior border of the pubic hair extended upwards and the clitoris was slightly enlarged The voice had also become lower

An androgen producing ovarian tumour was assumed and in March 1055 i e after 19 months amenorrhœa a right oophorectomy was performed The operative specimen was the size of a tangerine The ovary had been largely replaced by a well defined firm almost fibrous tumour with a yellow cut surface

Histological examination The tumour was of fairly complex appearance It was built up mainly of solid columns of polygonal fairly amorphous cells with a moderate amount of sudanophilic material In some areas there were clear trabecular structures with a central loosening of the trabeculæ in other areas there were distinct adenomatous structures with a cubical to cylindrical epithelium and the tubules were surrounded by well defined connective tissue stroma Small groups of cells with round dark nuclei and abundant pale cytoplasm resembling Leydig cells were also seen The tumour

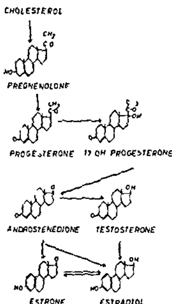


Fig 3 Biosynthesis of testosterone estrone and estradiol

Discussion

Recent *in vitro* investigations have shown that the biosynthesis of the sex hormones in the gonads very probably occurs according to the following series of reactions acetate → cholesterol → pregnan-5-en-3-ol-20-one → progesterone → 17-OH-progesterone → androst-4-ene-3 17-dione (Bagett *et al*, 1956, Slaunwhite *et al*, 1956, Solomon *et al* 1956, Savard *et al*, 1957, Viscelli *et al*, 1957 Lynn *et al*, 1958 Savard *et al* 1961) (see Fig 3) Zander (1957, 1958) also isolated the last two of the above mentioned steroids from follicular fluid and corpora lutea and thereby confirmed the *in vitro* observations The first stages in the biosynthesis of steroids thus appear to be the same in the ovary and in the testis, after which the specific distribution of different enzymes and enzyme systems results in the specific final products of the gonads œstrogens and testosterone respectively (Samuels *et al* 1951) Testosterone and andro-

normal (from 20 1 to 11 7 mg/24 hours) The DF, which was found to be markedly elevated before operation, also fell markedly but was still moderately increased one year after the operation The values found for œstrogens (bio-assay) and gonadotrophins in February 1954 were normal (Table I)

Table I *Determination of Total Neutral 17-KS, DF and 17-KGS in Urine*

Date	17 – KS		Ketogenic Steroids mg/24 hrs	Remarks
	Total mg/24 hrs	DF mg/24 hrs		
1954 Feb 2	14 4	2 0		During amenorrhœa Œstrogens 120 MU/24 hrs Gonadotropins 10–40 MU/24 hrs
1955 March 2	20 1	2 6		During amenorrhœa
4	Oophorectomy			
20	11 7	1 2		
June 21	10 4	1 8	10 6	26th c d
1956 May 22	6 8	1 2	10 4	Pregn 27th week
1957 Feb 26	6 0	0 6	12 6	Partus 31st Aug 1956 No mens since
Normal value	4 5–14 0	0 2–0 6	4 5–14 0	

Table II *Cases of Increased Excretion of 17-KS in Arrhenoblastoma Ovarii*

Author	Year	17 – KS mg/24 hrs
Cohen M *et al*	1958	14 1–10 8
Dorfman R I and Shipley R A	1956	41 2
Greenblatt R B	1955	31 7–37 6
Herbert P M *et al*	1956	25 3
Jones, G S *et al*	1946	36 0–56 0
Lobotsky J *et al*	1954	12 0–90 0
Ott B	1954	17 8–25 1
Sele V	1960	14 1–18 3
Smiley J *et al*	1953	64

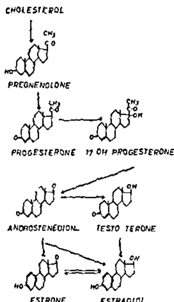


Fig 3 Biosynthesis of testosterone estrone and e-tradiol

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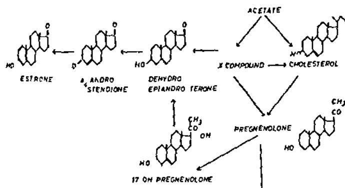


Fig 4 Biosynthesis of estrone from dehydroepiandrosterone (After Antognetti)

In view of the increase of DF in the above mentioned case it would be of interest to know whether virilism of ovarian origin in an enzymatic dysfunction may occur in an earlier phase than that described The question bears on the synthesis of œstrogen from DHEA Although this substance does not appear to be a metabolite or any precursor of corticosteroids (Lieberman 1956), its occurrence in the urine has been regarded as a measure of adrenocortical activity Various investigations appear to show that the DHEA is not a metabolite of testosterone, on the other hand it is a precursor in the testosterone synthesis in the adrenals, and it is metabolized partly to androsterone and etiocholanolone, and partly excreted in unchanged form in the urine (Short, 1960) Whether part of the DHEA of the urine in disease may be derived from the gonads and be a precursor of the œstrogens is however not known If it is it would be synthesized via DHEA – androstenedione (see Fig 4) and a limited possibility of the introduction of the double bonds in the A ring would result in an increase of DHEA and androstenedione A feature common to different types of ovarian hyper androgenism would thus be a partial or a total lack of the possibilities of the linkage of double bonds in the A ring

A question that then arises is What help can be expected from determination of the total neutral 17 KS in the urine in the

stenedione have been isolated from a normal human ovarian homogenate and identified by the isotope technique Thus, judging from *in vitro* experiments, œstrogens can be formed from testosterone (Meyer, 1955, Wotiz *et al*, 1956, Engel, 1957, Bagett *et al*, 1959) In the ovary then, œstrogens are synthesized via 17-OH-progesterone→androstenedione (→testosterone), conversion of androstenedione to œstrone (Engel, 1957) and of 19-OH-androstenedione to œstrogens (Meyer, 1955) is well known The conversion of œstrone to œstradiol and *vice versa* has been shown to occur in a number of different tissues (Engel, 1957) The presence of traces of androgens in the ovary and of œstrogens in the testis may therefore be regarded as normal The difference between the ovary and the testis regarding the synthesis of steroids should thus be quantitative rather than qualitative

The evidence suggests that the virilism in arrhenoblastoma is due to an overproduction of androgenic steroids secondary to disorders of the steroid synthesis in the tumour tissue On incubation with arrhenoblastoma tissue progesterone-4-C^{14} is metabolized to 17-OH-progesterone and androstenedione (Wiest *et al*, 1959, Savard *et al*, 1961) It therefore seems likely that the formation of androgens in this ovarian tumour resembles the biosynthesis of testosterone and androstenedione from progesterone in the normal male gonads (Slaunwhite *et al*, 1956) This, however, presupposes that the progesterone is formed by the tumour, a condition which appears to have been confirmed by Anliker *et al* (1957), who isolated progesterone, testosterone, androstenedione and androsterone from arrhenoblastoma tissue Metabolically then, arrhenoblastoma should not differ qualitatively from normal ovarian tissue However, in arrhenoblastoma the introduction of double bonds in the A ring is partly or completely inhibited with a consequent accumulation of precursors with weaker or stronger androgenic properties The occurrence of œstrogens in the urine may be due to the formation of such œstrogens in the tumour, (a relative insufficiency of the formation of œstrogen) in the remaining ovarian tissue or in the healthy ovary, then the urine contains normal amounts of œstrogenic substances together with their precursors resulting in a preponderance of these androgenic precursors

sterone if it is to produce a demonstrable increase in the total urinary 17-KS

Testosterone is the biologically strongest human androgen, androstenedione is only 3-6 per cent as active (Savard *et al*, 1961) DHEA is a much weaker androgen and 17-OH-progesterone is a very weak androgen It has been suggested that it is not 17-OH-progesterone that is active but its androgenic metabolites (Short, 1960) It is metabolized partly to androsterone and partly to etiocholanolone One of its main metabolites is pregnantriol and the determination of pregnantriol in the urine is therefore useful in the assessment of the formation of 17-OH-progesterone While virilism of adrenal origin is believed to be due mainly to the weaker androgens, androstenedione, androsterone, DHEA and 17-OH-progesterone, virilization in arrhenoblastoma is often due to an increased formation of testosterone, which is a strong androgen, and to a certain extent also of androstenedione Accordingly, the same degree of virilization of adrenal origin requires a greater production of the weaker androgens and consequently higher values for the total 17-KS in the urine than virilization in arrhenoblastoma In addition, in virilism of adrenal origin the DHE level is higher than in arrhenoblastoma, there is often also an increase of the C-21-steroids in the urine because of an increase of the 17-OH-progesterone metabolite, 3α, 17α, 20α pregnantriol

It is clear from what was said above that determination of the urinary 17-KS is useful in the diagnosis of arrhenoblastoma Virilization of a woman with normal or only moderately increased excretion of 17-KS suggests the presence of an arrhenoblastoma If the 17-KS values are markedly increased the virilism is probably of adrenal origin, particularly if the urinary DHEA is also excessive An increase of the urinary C, steroids in the form of pregnantriol also argues for virilism being of adrenal origin In borderline cases the differential diagnosis is difficult and the steroid pattern is non informative Historical data and palpation may be helpful Peritoneoscopy or surgical exploration is sometimes necessary, and should perhaps be done in all cases of virilism in which the urinary steroid pattern does not give a clear-cut diagnosis particularly since the urinary steroid

diagnosis of arrhenoblastoma? These steroids represent a structurally and biologically heterogenic group of steroid metabolites Some 25 per cent consist of the 11-oxygenated-17-KS and 75 per cent are so-called 11-desoxy-17-KS, of which the most important are androsterone, etiocholanolone and DHEA If virilization in arrhenoblastoma is due to an increased production of androgenic substances, one would expect an increase of the urinary neutral 17-KS But, judging from the literature, no such increase is demonstrable Of the 26 cases of arrhenoblastoma with virilization, in which the total neutral 17-KS were determined, the level was elevated in 9, but in the remainder it was normal (Fig 5) This has been tentatively explained by the assumption that the androgenic substances formed by the tumour are not metabolized to 17-KS but to catabolytes, which present methods cannot identify among the neutral 17-KS in the urine (Dorfman and Shipley, 1956)

Recent investigations with fractionation analysis of the urinary 17-KS do not seem to confirm this assumption In normal males the urinary 17-KS are derived mainly from the adrenal cortex and to a certain extent from the testis, in normal females, practically entirely from the adrenal cortex Of the urinary 17-KS, androsterone and etiocholanolone are of particular interest because they are the most abundant and the main metabolites of testosterone and androstenedione According to recent investigations they may also be derived from other sources, particularly from DHEA, which is thus excreted mainly as androsterone and etiocholanolone and to some extent unchanged It now also appears that DHEA is the main precursor of the urinary androsterone and etiocholanolone (Vande Wiele, 1960) The contribution by the testicular precursors is, in other words, less than what was originally supposed, Gallagher (1960) found the daily production of testicular testosterone to be less than 3 mg, of which 1-1 5 mg is excreted in the urine as 17-KS, i e less than 10 per cent of the total urinary 17-KS Even if the ovaries secreted an equal amount of testosterone, it would only increase the urinary 17-KS by 1-1 5 mg/24 hours Owing to the wide variation in the amount of total 17-KS excreted in the urine, an arrhenoblastoma must produce large amounts of testo-

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patterns of other androgenproducing ovarian tumours resemble that seen in adrenal hyperplasia and adrenal tumours

SUMMARY

A description is given of a case of virilization resulting from an arrhenoblastoma of histologically intermediate form in a previously healthy 28-year old woman with regular and apparently ovulatory bleedings The urinary excretion of neutral 17-keto steroids and DF was somewhat increased before operation, the total 17-KS returned to normal within 2 weeks of the operation, but the DF was still elevated one year later

The underlying mechanisms of virilization and the possibilities of diagnosing arrhenoblastoma preoperatively are discussed

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TORSION OF THE FALLOPIAN TUBE

A Clinico pathological Study

BY

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Torsion of the Fallopian tube is one of the very uncommon gynæcological complications Since the publication of the earliest cases by Bland-Sutton (1890) and Delbet (1898) examples have appeared sporadically in the literature

Torsion may affect the normal tube or the tube which is the seat of hydrosalpinx and it seems that pregnancy may predispose to this complication, for many of the reported cases occurred in gravid women Torsion of the normal tube during pregnancy has been described by several authors (Aulhorn, Caldwell, 1949, Gaujoux and Gaujoux, 1955, Kushner and Rosenbaum, 1952, McKerrow, 1934, Savage, 1936, Vermelin *et al*, 1955), and torsion of hydrosalpinx during gestation was reported by others (Eastman, 1927, Hartmann, 1900, Peraire, 1912, Pinard, Ward, 1910)

Among the interesting reports on torsion of the normal tube in the non pregnant state the papers by McIlroy (*1910*), Cassidy and Norbury (1911), Stark (1911), Michael (1924), Auvray (1929), Neel *et al* (1943), Michaelson (1948), de Soldenhoff (1949), Abbas (1955), Kohl (1956), Keller and Keller (1959), Humphreys (1960) and Lygonis (*1960*) deserve special mention Anspach (1912), Eastman (1927),



Fig 1 Twisted right tube Tubal wall markedly thickened and dark blue in colour Note normal fimbriæ and absence of adhesions

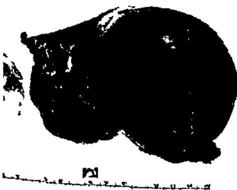


Fig 3 Twisted left tube and ovary The tube is markedly dilated and the ovary is enlarged Both organs are gangrenous Note preservation of tubal fimbriæ and absence of adhesions A cystoma simplex removed from right ovary is also shown



Fig 7 Twisted left parovarian cyst with stretched elongated tube and ovary sharing in the twist Note dark reddish blue colour of the twisted structures

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Goldberg (1938) and Thomas (1954) described instances of torsion of hydrosalpinx in the nongravid woman Wolf (1951) described a unique case of torsion of a tuberculous pyosalpinx

Bilateral torsion of the Fallopian tube is exceedingly rare Anspach (1912) collected 7 cases, since then Senechal (1932), Pineda (1934), Ficklen (1938), Shaw (1949) and Herve (1957) reported similar instances

A few authors have attempted to review the literature on the subject of tubal torsion The first collective studies on torsion of hydrosalpinx were published in 1899 by Præger and in 1901 by Cathelin Anspach (1912) collected 95 cases of tubal torsion, 62 being cases of twisted hydrosalpinx Eastman (1927) brought the number of cases of twisted hydrosalpinx up to 91 Regad (1933) who reviewed 201 cases of tubal torsion found that in 24 per cent there was a hydrosalpinx, in 12 per cent of all cases the condition occurred in pregnancy Savage (1936) collected 13 published cases of twisted Fallopian tube during pregnancy and added one of his own Goldberg (1938) stated that up to that time 104 instances of twisted hydrosalpinx had been reported, including his own case In 1951 Wolf estimated that just over 120 cases of twisted hydrosalpinx had appeared in the literature

Material

During the past 10 years the authors have encountered 6 examples of torsion of the Fallopian tube These cases, none of which has been reported before will be described They illustrate almost every known variety of this clinico pathological entity

Case I

A multigravida 35 years old pregnant 36 weeks was admitted to hospital in June 1954 complaining of intermittent colicky pain in the right lower quadrant of the abdomen On the day after admission the pain became much more severe and radiated to the right inguinal region as well as to the right loin Nausea was pronounced but vomiting occurred only once The pulse rose from 90 to 110 and the temperature was 37 2 C There was marked tenderness in the right iliac fossa The uterus corresponded to the size of 36 weeks pregnancy Presentation was cephalic and the head was not engaged On vaginal examination the only abnormality detected was the presence of marked

markedly thickened and is the seat of diffuse hæmorrhage Leucocytic infiltration mainly with lymphocytes is evident Numerous giant cells and few tubercle like formations are also seen (Fig 2) There is marked degeneration of the tubal epithelium

Case II

A multipara 32 years old married for 15 years was admitted in February, 1961 She complained of intermittent pain in the left loin radiating to the left iliac fossa Menstrual history was normal and the last period had ceased seven days before admission Shortly after admission she started to have vaginal bleeding which was slight but persistent The general condition was good temperature was 37 C pulse 100 and blood pressure $\frac{110}{60}$ mm Hg

There was tenderness and rigidity in the lower abdomen especially in the left iliac fossa Vaginal examination revealed the presence of a left cystic adnexal mass the size of an orange which was exquisitely tender On the right side a smaller cyst was felt which was mobile and not tender The posterior fornix was clear and the uterus was normal in size and position Urine examination was negative and the blood picture was normal In view of these findings a provisional diagnosis of left renal colic made on admission by the house surgeon was changed to one of twisted left ovarian cyst

Laparotomy was done on the third day after admission at which time the temperature was 37 8 C and the pulse 120 The uterus was found to be normal The left tube was twisted clockwise by one and a half turn and formed a dark blue cystic mass the size of a big orange without any adhesions to the surrounding structures The twist occurred at the tubo-uterine junction The left ovary was involved in the torsion process and was gangrenous Left salpingo-oophorectomy was done The right tube was also found to be twisted clock wise but only by half a circle It was congested but not distended The right ovary was the seat of a small cystoma simplex and had come to lie in front of the uterus Although it thus seemed to have initiated the tubal torsion the ovary did not share in the twist On undoing the twist the tube regained its normal colour ovarian cystectomy was done and the right ovarian ligament was plicated

Pathological Report The left Fallopian tube is markedly distended with serosanguinous fluid and its wall is dark reddish blue in colour The fimbriæ are present but adherent at their base closing the tubal ostium The ovary is enlarged and gangrenous and is adherent to the tube (Fig 3) Histologically the tubal wall is composed of fibrous tissue and the blood vessels show marked dilatation and engorgement with extravasation of blood in the tubal wall (Fig 4) The tubal epithelium is not recognizable The cyst removed from the right ovary (Fig 3) is a cystoma simplex



Fig 2 Histologic section of wall of twisted tube shown in Fig 1 Diffuse hæmorrhages and leucocytic infiltration mainly with lymphocytes are seen. There are also foreign body giant cells with an occasional imperfect tubercle-like formation Note degenerated tubal epithelium x 115

tenderness in the region of the right fornix The leucocytic count was 10,000 A diagnosis of acute appendicitis was made

The abdomen was opened by a McBurney incision and a bluish red swelling immediately presented itself into the wound This was found to be the right Fallopian tube which had undergone a threefold anti-clockwise twist and was frankly gangrenous The site of torsion was at the junction of the outer two thirds and inner third of the tube where a thin band of adhesion was found The ovary was not included in the twist and the left adnexa was normal Right salpingectomy was carried out

Pathological Report The tube is markedly thickened and is dark blue in colour (Fig 1) The fimbrial end looks normal and the tubal wall shows no adhesions On section of the tube the lumen is found to contain a small amount of hæmorrhagic exudate Microscopically the tubal wall appears



Fig 5 Cut sect on of twisted left tube The tube is distended and dark bluish red in colour The tubal fimbriæ are retracted

ovary was normal and did not take part in the twist A thin peritoneal band was adherent to the site of the twist The left adnexa was normal Right salpingectomy and myomectomy was performed

Unfortunately pathological study of the removed Fallopian tube was not made

Case IV

A mult para 40 years old was seen in private practice in January 1961 just before the expected date of her period She complained of intermittent colicky pain in the left side of the abdomen of 6 months duration The pain was initially slight but during the last month it had been much more severe with radiation to the loin and to the vulva Recently the patient had also experienced frequent and painful micturition She had been seen by a general surgeon who had made a diagnosis of left renal colic but examination of the urine and radiographic examination of the urinary tract gave completely normal find ngs

On examination the patient was obese (we ght 115 kg) Her general condi tion was very good the pulse temperature and blood pressure were normal A very tender cystic swelling the size of a grape fruit was felt in the umbilical reg on The left loin was also tender to palpation On vaginal examination the uterus was normal but moving it elicited marked tenderness Because of the obesity the adnexæ could not be felt A diagnosis of twisted ovarian cyst was made and laparotomy was performed

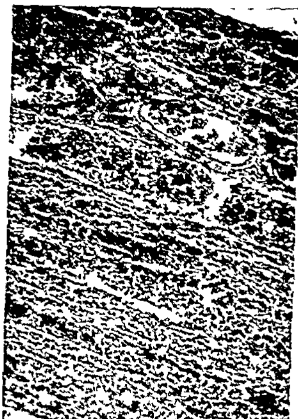


Fig 4 Histologic section of wall of tube shown in Fig 2 Note dilated engorged vessels and marked extravasation of blood in tubal wall X 90

Case III

A nullipara, 35 years old, was admitted to hospital in July 1954 complaining of abdominal swelling and intermittent pain in the right lumbar region and right iliac fossa She also complained of menorrhagia and primary sterility

On examination the temperature was normal but the pulse was 100 A pelvi abdominal mass was felt reaching about two fingers above the umbilicus On bimanual examination this proved to be the uterus enlarged by the presence of multiple fibromyomata Tenderness was elicited a few centimeters above McBurney s point Shortly after admission the pain became progressively more severe and the pulse more rapid The diagnosis of acute appendicitis and multiple uterine fibroids was made

At laparotomy the diagnosis of uterine fibroids was confirmed but the appendix was normal The right tube was twisted by 2 full turns at the junction of its outer two thirds and inner third and was gangrenous The

menstruation had been regular but she had amenorrhoea for 8 weeks before admission

On examination the general condition was good the temperature 37 C the blood pressure $\frac{110}{80}$ mm Hg and the pulse 100 Abdominal examination revealed tenderness and slight rigidity in the left iliac fossa On vaginal examination the physical signs of a 10 weeks uterine pregnancy were elicited There was severe tenderness in the region of the left fornix and a tender cystic mobile mass the size of an orange was felt to the left side of the uterus A diagnosis of a twisted left ovarian cyst with pregnancy was made

At laparotomy there was a twisted simple cyst of the left ovary which was dark red in colour The left tube was also twisted by almost a full turn and was also dark red in colour The tubal twist was undone whereupon it gradually regained its normal colour and ovarian cystectomy was performed The pregnant uterus and other adnexa were normal The patient was kept in hospital for one month after operation during which time the pregnancy continued undisturbed

Case VI

A multipara 27 years old was admitted in February 1952 complaining of sharp pain which had started suddenly when she was lifting a heavy weight The pain was first localised to the left lower quadrant of the abdomen but was later described as radiating to the left loin The attack occurred 4 days before the expected date of the menstrual period and a few hours after the onset of pain vaginal bleeding was noticed

On examination the general condition was good temperature 37 C pulse 90 and blood pressure $\frac{120}{80}$ There was marked tenderness but only slight rigidity in the left iliac fossa On vaginal examination the uterus was normal in size and position and a cystic tender tumour was felt to the left side of the uterus The posterior fornix was clear The diagnosis of twisted left ovarian cyst was made and laparotomy was undertaken

A twisted hæmorrhagic cyst was found to the left side of the uterus and the left Fallopian tube was twisted by two full circles and was gangrenous The left ovary was separate from the cystic tumour but took part in the process of torsion and was markedly enlarged and dark blue in colour The left tube and ovary were removed together with the cystic tumour which proved to be a broad ligament cyst

Pathological Report The specimen consists of a large parovarian cyst which is dark reddish blue in colour The Fallopian tube is stretched on the top of the cyst and is sharing in the gangrenous process The ovary is enlarged cystic and infarcted (Fig 7) Histologic examination of the tubal wall shows marked congestion and blood extravasation The folds of the tubal mucosa are preserved but the lining epithelium is flattened out in areas (Fig 8)

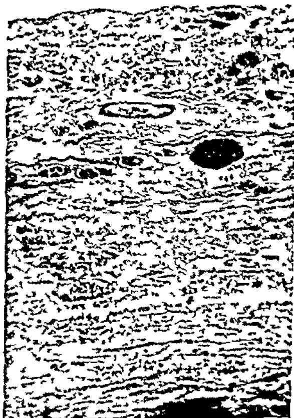


Fig 6 Histologic section of wall of tube shown in Fig 5 Note dilatation and engorgement of the vessels and extravasation of blood × 68

The cystic swelling proved to be the left Fallopian tube which was twisted by two and a half turns distended with blood stained fluid bluish black in colour and lying unusually high in the abdomen The corresponding ovary contained a small simple cyst the size of a lemon but did not take part in the twist The uterus and other adnexa were normal Left salpingo-oophorectomy was carried out

Pathological Report The tube is markedly distended with serosanguinous fluid Its wall is dark bluish red in colour The fimbriae are retracted and the abdominal ostium is sealed (Fig 5) The ovary contains a cystoma simplex Histologically the tubal wall is fibrotic and the lining epithelium cannot be recognized The blood vessels are dilated and engorged with extravasation of blood in the tubal wall (Fig 6)

Case V

A nullipara 17 years old was admitted in October 1960 complaining of pain in the left iliac fossa radiating to the back and suprapubic region Her

cases in which the twisted tube was dilated this seemed to have been the result of the torsion rather than its cause (vide infra)

Extrinsic causes which may predispose to torsion of the tube include (1) *Changes in the neighbouring organs such as tumours of the ovary or parovarium* (Keller and Keller, 1959), *omental or other adhesions to the outer part of the tube* (Michon, 1930, Shaw, 1949), and *enlargement of the uterus by pregnancy or tumour* The findings in our patients suggest that this factor, i e changes in the neighbouring organs, is by far the most important in the ætiology of tubal torsion In our cases II, IV, V and VI a tumour of the ovary or the broad ligament was present In cases I and III adhesions were found at the site of the tubal twist The ætiologic significance of enlargement of the uterus has not been emphasized in the literature but we believe it was of importance in three of our patients namely, Cases I and V who were pregnant, and Case III who had multiple fibromyomata (2) *Mechanical factors such as movements and contractions of neighbouring hollow viscera* (Keller and Keller, 1959), *sudden body movements and trauma to the abdominal wall* (Blum and Sayre, 1937, Humphreys, 1960, McIlroy, 1910) Such an effect may have precipitated the twist in our case VI who had sharp pain of sudden onset when lifting a heavy weight in this patient, however, a broad ligament cyst was present without which the accident might not have taken place (3) *Pelvic congestion* This seems to be of some importance in predisposing to tubal torsion as shown by the fact that this accident often occurs at the time of ovulation or in the immediate premenstrual period (Abbas, 1955 Herve, 1957 Keller and Keller, 1959) Eighty per cent of cases of torsion of the tube are said to have occurred in women of child bearing age and most of the remainder have affected girls at the menarche In two of our non pregnant cases the patient was seen in the immediate premenstrual period (Cases IV and VI) Apart from the mechanical effect of enlargement of the uterus the frequency of tubal torsion during pregnancy (our Cases I and V) may also in part be due to the concomitant pelvic congestion The significance of the hæmodynamic factor in the ætiology of this complication has been stressed by Keller and Keller (1959) who carried out interesting experiments to illustrate this point

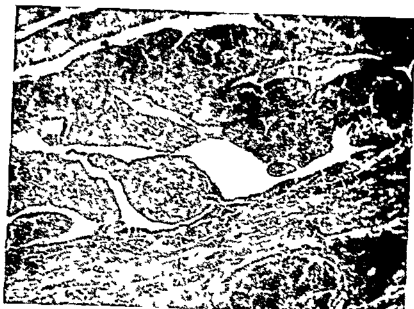


Fig 8 Histologic section of wall of tube shown in Fig 7 Note marked congestion and extravasation of blood in the plicæ of the mucosa and in the muscle layer Tubal epithelium is recognizable but is mostly flattened out. × 58

Discussion

Aetiology

The causative factors in tubal torsion may be intrinsic or extrinsic

Intrinsic causes, i e abnormalities of the tube itself which are said to favour torsion, include (1) Congenital tubal anomalies, such as excessive length (Keller and Keller, 1959), tortuosity, (Herve, 1957), spiral course (Neel, 1943), and a long mesosalpinx which does not extend well laterally to the tubal fimbriæ (Kohl, 1956), (2) Acquired pathology, such as swelling of the tube (Keller and Keller, 1959) by hydro or hæmatosalpinx, tubal neoplasms and previous surgery on the tube such as Pomeroy's operation of sterilization (Kohl, 1956) and (3) Abnormal peristalsis of the Fallopian tube which may be due to autonomic dysfunction (Michon, 1930, Blum and Sayre, 1937 Herve, 1957) These intrinsic factors are theoretically attractive but do not seem to have played a significant role in our cases, in the 2

reported cases of twisted hydrosalpinx were in reality instances of torsion of a previously normal tube

As already stated, bilateral torsion of the tube is extremely rare, only 12 cases have been reported Our case II in this series is the thirteenth example in the literature Torsion seems to affect more commonly the right than the left tube Shute (1932) found that the right tube was involved in 68 per cent of the cases he reviewed As mentioned above, this is believed by Keller *et al* (1956) to be due to the physiologic right sided torsion of the uterus Neel *et al* (1943) on the other hand believe that the right sided preponderance is more apparent than real and is explained by the surgeon being more prone to operate in the presence of right sided pain We are inclined to agree with this latter view Of our 5 cases of unilateral torsion the right tube was affected in 2 and the left in 3, and it is noteworthy that in the 2 cases in which the right tube was involved the operation was performed on the diagnosis of acute appendicitis (Cases I and III)

The degree of torsion in the reported cases varied from half a twist, i e 180° (Herve, 1957) to 5 twists (Wolf, 1951) The severer the degree of torsion the more likely is gangrene to develop quickly According to Abbas (1955) the degree of torsion of the tube and consequently the amount of interference with its blood supply and the development and extent of gangrene, are important in determining the severity of the symptoms and signs These factors are also of importance with regard to the possibility of saving the organ In our Case V the tube was twisted by less than a full circle and was markedly congested but after undoing the twist it regained its normal colour and was not removed In our Case II in which the right tube was twisted by only half a circle the twist was undone and the tube was conserved the left tube which was twisted by one and a half circle was gangrenous and had to be removed In a similar case of bilateral torsion reported by Hervé the left tube was twisted by 360° and was tense and infarcted and had to be excised but the right tube twisted by only 180° was lax and not infarcted and was therefore left behind

In some of the reported cases a cyst or tumour was present in the ovary or broad ligament on the affected side The ovary nor

Pathology

Some authors have denied that the normal tube can undergo torsion (Smith and Butler, 1921, Herve, 1957) Others, (Keller and Keller, 1959), have maintained that torsion can definitely affect the normal tube Darner, (1962) believes that torsion does sometimes affect the normal tube but much less commonly than the diseased organ Several authors stress the difficulty of settling this question Histological examination of the twisted tube was only performed in a few of the reported cases (Shute, 1932) Even when histologic examination is carried out, evidence of previous tubal pathology may often be obscured by the changes in the tubal wall produced by torsion On the other hand, tubal torsion may induce pathologic changes in the wall of the organ which closely simulate those caused by inflammation

The findings in our cases suggest not only that torsion can affect the normal tube but also that this probably occurs more commonly than torsion of the diseased organ In four of our patients (Case I, Case II, right side, Case III and Case V), the tube was grossly normal and was not distended, and in two of them (Case II, right side, and Case V) the condition was treated conservatively by undoing the torsion and preserving the tube In Case I histologic examination showed leucocytic infiltration and giant cell formations in the wall of the tube but this was clearly the result of the torsion process and not of previous inflammation for the patient had no history of pelvic infection, the affected tube was mobile and free from any adhesions, the other tube was normal and, most significant, the accident occurred during pregnancy

In two of our patients (Case II, left side, and Case IV), the twisted tube was distended with serosanguinous fluid Although the condition simulated a hydrosalpinx, we believe that this was probably the result of the torsion process which, if gradual or intermittent, may lead to occlusion of the tubal ostium with subsequent distension of the affected organ In both patients there was no history of pelvic infection, the other adnexa was normal and the affected tube was mobile and free from adhesions and histologic examination of its wall showed no evidence of chronic inflammation In view of these findings, it is our opinion that many of the

Vermelin *et al*, 1955, Kohl, 1956) The very frequent presence of loin pain in the previously reported cases (and our own Cases I, II, IV and VI) is remarkable and should help in differentiating this condition from torsion of an ovarian tumour The reason for the frequency of loin pain in torsion of the tube but not ovarian tumours awaits explanation This type of pain and the occasional presence of other symptoms referable to the urinary tract (Mc Kerrow, 1934, Thomas, 1954, Abbas 1955) account for the fact that tubal torsion is often mistaken for renal or ureteric disease (our Case IV) Examination of the urine radiography and other urologic investigations should help to exclude pathology of the urinary system

Other than pain, few symptoms are caused by tubal torsion Nausea with or without vomiting may be present, but seems to be uncommon It was severe in only one of our 6 patients (Case I)

Uterine bleeding followed the onset of pain in the cases reported by Abbas and de Soldenhoff and may be explained by the associated pelvic congestion This symptom was present in our Cases II and III

The abscence of shock and the good general condition of the patient (Eastman, 1927, Thomas, 1954 Kohl 1956 Herve, 1957) in the presence of severe pain is usually striking and is well demonstrated by our case histories This should help to differentiate tubal torsion from such conditions as twisted ovarian tumour or bleeding ectopic gestation The pulse and temperature are usually normal at first (Eastman 1927, Vermelin 1955, Herve 1957) but later may be slightly elevated (Shaw 1949 Thomas, 1954, Kohl 1956) Leucocytosis is often present but is seldom marked (Goldberg and Olin 1938 Shaw, 1949) These latter points are useful in distinguishing the condition from acute appendicitis and acute salpingitis

On examination of the abdomen tenderness may be present in the iliac fossa (Shaw 1949), in the loin (Vermelin 1955) or in both (our Cases I II V and VI) Tenderness is as a rule slight especially in early cases (Shaw 1949 Kohl 1956) and is much less marked than in other acute abdominal conditions Sometimes the point of tenderness is rather high (Vermelin, 1955) in our Case IV there was tenderness in the loin and in the umbilical

mal or abnormal, may or may not be involved in the process of torsion Auvray (1929) in a review of 14 cases of tubal torsion found that the ovary was affected in 9 The ovary was also stated to be involved in the cases reported by Gaujoux, (1955) by Neel *et al* (1943) and by Goldberg, (1938) On the other hand, the ovary was specifically stated to be healthy and not to have taken part in the process of torsion in the cases reported by Herve (1957), Vermelin (1955), Eastman (1927), Thomas (1954) and de Soldenhoff (1949) In the case reported by Kohl (1956) a cystic right ovary was present which the author believed to have predisposed to the initiation of tubal torsion but which was itself not twisted In Shaw's (1949) case of bilateral tubal torsion the left ovary was the seat of a dermoid cyst and the right ovary was studded with small cysts but neither ovary shared in the process of torsion

In two of our own cases (Cases I and III) the ovary was healthy and did not take part in the twist In case II, left side, an otherwise healthy ovary was twisted with the tube and was markedly infarcted In two cases (Case II right side and Case IV) the ovary was the seat of a *cystoma simplex* but was not twisted In Case V a cystoma simplex of the ovary was twisted and seemed to have predisposed to tubal torsion In Case VI torsion of the tube was definitely brought about by the twist of a broad ligament cyst and the ovary shared in the process of torsion

A careful consideration of these cases and those reported in the literature has not revealed any factor which governs the fate of the ovary in tubal torsion

Clinical Features

The most important symptom of tubal torsion is pain This is usually of sudden onset (Wolf, 1951, Kohl, 1956), and of paroxysmal or intermittent nature (Goldberg and Olin, 1938, Thomas, 1954, Vermelin, 1955, Herve, 1957) The pain is often present in the iliac fossa and may therefore, if right sided, simulate that of acute appendicitis (our Cases I and III), but classically it begins in or extends to the loin (Goldberg and Olin, 1938, Shaw, 1949, Kohl, 1956) and it may radiate to the pubis or to the thigh (Goldberg and Olin, 1938, Shaw, 1949,

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region but not in the lower abdomen Rigidity is as a rule absent early in the disease (Vermelin, 1955, Kohl, 1956), later, slight abdominal rigidity may occasionally be found (McKerrow, 1934, Shaw, 1949, Kohl, 1956) Rigidity was present in only two of our cases (Cases II and VI) The fact that rigidity is, as a rule, absent or not pronounced should help to differentiate the condition from such acute abdominal emergencies as acute appendicitis Occasionally a mass may be felt abdominally In our case IV a mobile, tender, cystic mass was felt in the region of the umbilicus

More commonly the twisted tube is only palpable on bimanual pelvic examination Occasionally the small mass produced by torsion of a normal tube cannot be detected except under anæsthesia (McKerrow, 1934) Tenderness on cervical manipulation is sometimes present (Kohl, 1956) In some cases Warneck's sign can be elicited, namely the feeling of the painful tense pedicle of the pelvic mass, especially on moving the uterus to the opposite side (Herve, 1957) Douglas's pouch is characteristically free from tenderness, unlike cases of ectopic gestation This feature was noted in all our cases

Cul de sac puncture may be negative or may yield some sero-sanguinous fluid but not frank blood Culdoscopy or peritoneoscopy may conceivably help in establishing the diagnosis, but no case has been reported in which either method was used

The above mentioned symptoms, signs and methods of examination should help to differentiate torsion of the Fallopian tube from such other abdominal emergencies as twisted ovarian tumour, disturbed ectopic gestation, acute salpingitis, acute appendicitis, pyelo ureteritis and calculus disease of the urinary tract Because of the rarity of tubal torsion, however, the correct diagnosis of this condition in the very large majority of reported cases was not made pre-operatively and the same has been true in all our six cases reported in this paper

Treatment

Torsion of the Fallopian tube is an acute abdominal emergency which calls for immediate laparotomy to establish the diagnosis and initiate the proper treatment The surgical procedure to be

carried out should depend on the exact pathology present If the tube is markedly abnormal, if the degree of torsion is pronounced, or if the tube is frankly gangrenous it should be excised On the other hand if the tube is reasonably healthy, if the torsion is by less than a full circle, and if on undoing the twist the organ is found to regain its normal colour and vitality it should be preserved and precautions should be taken to fix it in such a way as to prevent the possibility of recurrence of torsion An extensive study of the literature on this subject shows that this line of conservative treatment has hitherto received much less attention than it deserves In two of our cases (Case II, right side and Case V) the tube was conserved with no untoward after effects It is remarkable how rapidly the tube may regain its normal appearance after undoing the torsion and this is undoubtedly due to its rich and dual blood supply

We also believe that in many of the reported cases of tubal torsion the ovary was unnecessarily sacrificed The fact that it is usually technically easier to excise the ovary along with the affected tube should not tempt the surgeon to remove this important organ unless it is found to be irreparably damaged

SUMMARY

The literature on torsion of the Fallopian tube is reviewed and six new cases of this very rare entity are described in detail The ætiology and the pathology of the condition are discussed It has been the authors experience that extrinsic factors particularly changes in the neighbouring organs, play a very significant role in predisposing to torsion of the tube The authors also believe that torsion affects more commonly the normal than the abnormal tube and that pathological distension of the organ is more often the result than the cause of torsion

The clinical features produced by tubal torsion are presented and the frequency of pain occurring in, or radiating to the loin is stressed Pain in the iliac fossa is also frequent and when right sided it often causes the erroneous diagnosis of acute appendicitis to be made

Immediate laparotomy is always called for but the affected tube

need not always be removed The indications for conservative treatment by undoing the twist and preserving the tube are outlined Whenever possible the ovary on the affected side should be saved This conservative approach to the treatment of tubal torsion has not heretofore received the attention it deserves

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THE RHESUS FACTOR AND CANCER OF THE FEMALE GENITAL TRACT

BY

PER BERGSJÖ AND PER KOLSTAD*

Publications in recent years concerning a possible correlation between blood groups and cancer have mainly been concerned with the AB0 system In studies on the Rhesus factor and cancer of the colon, rectum, breast, bronchus, pancreas and œsophagus in Great Britain, Aird *et al* (1954, 1960) found no significant difference in the genotype D distribution as correlated with the normal population In previous work on the AB0 blood groups and cancer of the uterine cervix (Flottorp, Hausken, and Kolstad, 1960), the Rhesus factor frequency in a series of 741 patients with cervical carcinoma was mentioned, but no comparison with the distribution in the general population was made

The present study is an investigation into the frequency of the Rhesus genotype D in 493 patients with cancer of the uterine body and in 397 patients with cancer of the ovary In addition we have included the above-mentioned series of 741 women with cancer of the cervix All these patients have been treated at The Norwegian Radium Hospital during the years 1953 to 1960 Since 1959 blood groupings have been performed on all patients on admission Prior to that year blood group determinations were made on surgical patients and on those who needed blood transfusions for other reasons, this being the only selection in the series

Research fellow of The Norwegian Cancer Society

Histologically, the corpus cancer group consists of approximately 95 per cent adenocarcinomas including adenoacanthomas, and about 5 per cent sarcomas Of the ovarian tumours, slightly more than 80 per cent are adenocarcinomas and cystadenocarcinomas the rest being undifferentiated carcinomas, granulosa or theca cell tumours and less common types About 95 per cent of the cervical cancers are squamous cell carcinomas

The Rhesus genotype D distribution in the normal population has been taken from a publication by Hartmann, Brendemoen, and Brendemoen (1951), where the Rhesus genotypes of 1 000 blood donors in Oslo are given The patients in our series come from the whole country (70–75 per cent from the south-eastern part of Norway), but not significant variation in the Rhesus factor distribution within this geographical area has been found The frequency of the Rhesus negatives in our

Table I The Rhesus Factor Distribution in 493 Patients with Cancer Corporis Uteri Compared with the Distribution in the General Population

	Rh+		Rh−	
	No.		No	
Observed	422	85 6	71	14.4
Expected	408	82 7	85	17 3
Difference² / Expected no	0.48		2 19	

$\chi^2 = 2\ 67$ 1 degree of freedom. P $0\ 2 > \chi^2 > 0\ 1$
No significant difference

Table II The Rhesus Factor Distribution in 397 Patients with Cancer Ovarii Compared with the Distribution in the General Population

	Rh+		Rh−	
	No.	%	No	%
Observed	327	82.4	70	17 6
Expected	328	82 7	69	17 3

The distributions are almost identical

Table III *The Rhesus Factor Distribution in 741 Patients with Cancer Cervicis Uteri, Compared with the Distribution in the General Population*

	Rh+		Rh−	
	No	%	No	%
Observed	599	80.8	142	19.2
Expected	613	82.7	128	17.3
Difference² / Expected no	0.32		1.38	

$\chi^2 = 1.70$ 1 degree of freedom   P $0.2 > \chi > 0.1$
No significant difference

control series is also the same as in Great Britain, 17.3 per cent against 17.2 per cent (Aird *et al*, 1954)

Our findings are summarized in Tables I, II, and III In all three groups of patients the proportion of Rhesus negatives is within the range to be expected in the general population of Norway

SUMMARY

The frequency of the Rhesus genotype D has been studied in 493 patients with cancer corporis uteri, in 397 patients with cancer ovarii and in 741 patients with cancer cervicis uteri The proportion of Rhesus-negatives is within the range to be expected in the general population of Norway

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A CONTRIBUTION TO THE ÆTIOLOGY OF ECTOPIC PREGNANCY

BY

MIRJAM FURUHJELM, BIRGIT JONSON AND C.G LAGERGREN

It has long been recognized that there are certain correlations between infertility and ectopic pregnancy, and when ectopic pregnancies are examined malformations of the ovum are often found It has been debated whether these malformations should be assigned to malnutrition caused by the unfavourable site of implantation or to primary defects (Bayer, 1941 Dolff, 1944, Hormann 1949 Krone 1961) All authors seem to agree, that all defects observed could be explained by bad nutrition of the ovum during the transport through the oviduct or after implantation We have, however, found no reference to examination of the semen in cases of ectopic pregnancies

In a previous paper (Furuhjelm et al, 1962) we were able to demonstrate that in a series of 201 spontaneous abortions the quality of the semen was inferior to that in a control series of 116 cases of normal deliveries, suggesting that primary defects of the spermovum are of importance It therefore seemed justified to compare the quality of the semen in a series of ectopic pregnancies with our control series

Method

During the last 3 years we have requested semen specimens from the husbands of women who have been operated upon for

ectopic *pregnancy at our department. Up to now we have received* 23 such specimens The control series consisted of 116 specimens of semen from untreated husbands of married couples, who were examined because of infertility All of the women had normal living children within two years after the examination of the husband's semen Among the ectopic pregnancies the interval between the operation and the examination of the semen was less than two years in all cases

The ejaculate was collected by masturbation after an abstinence period of 5 days The quality of the semen was estimated by the concentration of spermatozoa and the percentage of morphologically abnormal spermatozoa

The differential count was made on 200 spermatozoa, using a phase contrast microscope Doubtful spermatozoa were counted at pathological and all specimens were examined by the same investigator (B J), the standard erreor of the spermatozoa count being 2 4 ± 0 2 per cent in duplicate determinations

The statistical calculations have been made according to the STUDENT s t test and the figures given are the mean ± the standard error of the mean

Results

Concentration of sperm spermatozoa In the control group a concentration of 138 7 ± 7 8 millions per cc was found and the corresponding figure for the ectopic pregnancies was 95 8 ± 12 0 millions per cc The difference 42 9 ± 14 3 millions per cc is significant, t = 3 0 and P < 0 001

Number of normal sperm spermatozoa per cc The mean number of normal spermatozoa in millions per cc was 96 3 ± 6 2 in the control series and 48 0 ± 7 0 for the ectopic pregnancies The difference 48 3 ± 9 4 being highly significant, t = 5 1 and P < < 0 001

Percentage of abnormal sperm spermatozoa In the control series the mean percentage of abnormal spermatozoa was 32 9 ± 1 1 and among the ectopics 50 3 ± 0 9 The difference 17 4 ± 1 4 being highly significant, t = 12 5 and P < 0 001

Discussion and Conclusions

From the result it is evident that the quality of the semen is inferior in the series of ectopic pregnancies It therefore seems probable that the proportions of primarily defective fertilized ova among this series of ectopic pregnancies was increased in relation to the control series and that such a primary defect might have caused some of the ectopic implantations

SUMMARY

A series of 23 ectopic pregnancies is reported in which the father s semen was examined. The quality of the semen among the ectopic pregnancies was inferior to a control series as judged from the concentration of sperm spermatozoa the number of normal sperm spermatozoa per cc and the percentage of abnormal spermatozoa The conclusion is reached that primary defects of the fertilized ovum can cause ectopic implantation

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ACUTE INTERMITTENT PORPHYRIA AND PREGNANCY

BY

HARRY ZILLIACUS AND HANNA KALLIO

Porphyria is a rare disease characterized by a disturbed pigment metabolism Red porphyrin pigments normally form the prosthetic group of respiratory enzymes such as catalase, cytochrome, and peroxidase In porhpyria there is partial block of the biosynthesis of these enzymes As a consequence, considerable amounts of porphyrin appear in the urine Of the different porphyrias the intermittent hereditary type is the most interesting from the obstetricians point of view, because 65 per cent of cases occur in women The onset is usually between 20 and 30 years of age The symptoms are mostly of gastrointestinal, neurological or psychological type Colicky or intermittent abdominal pains, vomiting, and obstipation are typical Paræsthesia or paralysis may occur in peripheral, cranial, or autonomous nerves Paralysis of the respiratory centre is a frequent cause of death (Rimington, 1952) The psyche of these patients is labile and hallucinations and psychoses are common Elevation of blood pressure, tachycardia, and amenorrhœa are reported to occur occasionally The dignosis is established when the urine contains porphobilinogen, which is the colourless precursor of porphyrin and which is regarded as pathognomonic, especially in this type of porphyria During the attack considerable amounts of uro- and coproporphyrin in the urine colour it red The prognosis of the disease is poor According to Waldenstrom, (1937) most of the patients die between the ages of 20 and 30

There is no specific therapy Sympathomimetic and parasympathomimetic drugs, vitamins, liver extract cortisone and ACTH have been administered to relieve symptoms Barbiturates initiate attacks of the disease

Case Report

The patient was a 27 year-old II gravida primipara No previous case of porphyria is known among members of the family At the age of 20 (1953) the patient visited an out patient clinic complaining of gastric pains for which she received citrus tablets In January 1957 the patient was admitted to hospital because of severe gastric pains vomiting and obstipation At an exploratory laparotomy the appendix was removed After the operation the dark urine was found to contain porphobilinogen uro-and coproporphyrin. Other investigations in 1957 included Blood count Hgb 87 per cent (Sahli) erythrocytes 4 350 cu.mm leucocytes 3 900 cu mm blood sugar 89 mg % Meulengracht 1 2 Daily excretion of coproporphyrin between 452 and 197 mg Uroporphyrin was once estimated quantitatively and found to be 544 mg per 24 hours Despite visual disturbances there were no pathological findings in the retinae Prostigmine and Mestinone therapy was prescribed The next attack of the disease occurred in September 1957 The patient spent one month in hospital Gastrointestinal symptoms dominated the clinical picture Pethidine Di Adresone Prostigmine and Mestinone were administered The porphobilinogen uro- and coproporphyrin tests were all positive and the urine coloured red Hgb 86 per cent (Sahli) leucocytes 3 500 cu.mm In april 1958 the patient was admitted to hospital for the third time She then had had dark-coloured urine gastric pains and obstipation at home for two weeks The last regular menstrual period had occurred in January 1958 At gynæcologic examination she was found to be three months pregnant There was notable tachycardia 110/min. Hgb 90 per cent leucocytes 6 800 cu mm porphobilinogen uro- coproporphyrin Schlesinger and Ehrlich tests positive The pregnancy was interrupted two weeks later at the Obstetrical and Gynæcological Department University Central Hospitals Helsinki In December 1958 the patient was again admitted to hospital complaining of considerable pain after an erroneous dose of barbiturates In October 1959 she was again in hospital because of pains vomiting, and obstipation The last menstrual period had been August 23 Excretion of coproporphyrin was 351 mg/24 hrs This time the patient wanted the baby and preferred to stay at home She remained in fairly good condition until February 1960 when a slight elevation of the blood pressure and oedema were found When still at home on March 27th she suddenly complained of severe headache and nausea On admission to hospital the same day the patient was found to be disorientated nearly blind or seeing double with muscular fibrillation and a blood pressure of 210/120 The fœtal heart

sounds were normal Despite administration of Largactil and hypertonic glucose infusion, one eclamptic convulsion occurred, which was controlled by administration of Evipan and opiates Four hours later the patient was able to speak normally With an intravenous Purovenin drip during the first two days Purovenin intramuscularly, and later occasional Largactil and Pethidine orally, it was possible to keep the blood pressure almost normal Laboratory tests Hgb 10 0 gr %, erythrocytes 3 360 cu.mm, leucocytes 6,700 cu.mm, hæmatocrit 21, Meulengracht 1 6, rest-N 40 mg %, alkali reserve 43 1 vol % CO_2, serum protein 6 7 per cent Proteinuria increased to 1 per mille Urine 250–1200 gr/day Although the period of gestation was only 33 weeks Cæsarean section was performed under epidural anæsthesia on April 9th because of the patient s relatively poor condition The infant a live boy weighing 1,460 gr, was discharged from the Children s Hospital 6 weeks later in good condition After the Cæsarean section a Purovenin drip again had to be instituted from time to time to control the blood pressure Periods of restlessness alternated with calmer periods From April 16 on, the patient again complained of pains in the abdomen and back Urinary output after the Cæsarean section decreased from 1,500 cc/day to 250 cc/day within a week On April 20th the patient was moved to the Department for Internal Diseases [1] Neurological examination showed spasticity of the right arm and leg, obviously due not only to the porphyria but to damage to the basia ganglia as a sequel of the eclamptic attack The porphobilinogen reaction remained strongly positive all the time but the general condition of the patient improved Her ability to speak increased, the muscular weakness decreased and mobility improved On May 29th however, the patient suddenly stopped speaking and expired within a few minutes At autopsy nothing pathological was found in the brain or spinal cord

Discussion

Pregnancy during acute intermittent porphyria is a rare occurrence Nesbitt (1944) reported two cases, in one of which the patient died subsequent to a spontaneous abortion Reidenberg and Farber (1955) presented a case in which the patient died two weeks after a Cæsarean section performed at the end of the sixth month of pregnancy Vine, Shaffer, Payley and Margolis (1957) reported a case in which the patient died two weeks after a spontaneous abortion These authors consider that the porphyria worsens considerably during pregnancy, possibly because of the frequent use of barbiturates O Dwyer (1955) reported one case, Durst and Krembs (1956) three

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cases Tricomi and Baum (1958) four cases, in which the delivery at expected term was normal and the condition of the mother good during the puerperium and later In 1961, Could, Allison and Bellew published a case in which normal delivery was followed by renewed attacks of porphyria two weeks later These authors found in the literature forty two cases of pregnancy in porphyric women In nearly all the cases there were attacks of the disease during pregnancy The mortality among the mothers, which was higher among the primiparæ amounted to 42 per cent Vine, Shaffer, Pavley and Margolis stress the importance of making the diagnosis of porphyria before the onset of pregnancy, because careless use of sedatives during pregnancy may worsen the porphyric state considerably O Dwyer believes it possible that a porphyric condition may improve as a result of changed hormonal balance initiated through pregnancy

In the case reported here the porphyria had commenced and been diagnosed several years before the first pregnancy which was interrupted In the course of both pregnancies there were severe attacks of porphyria during the first trimester During the second half of the second pregnancy there were symptoms of pre-eclampsia and eclampsia œdema considerable elevation of the blood pressure and proteinuria and one attack with convulsions and unconsciou ness after which the blood pressure remained high and the amount of protein in the urine increased There were none of the gastrointestinal symptoms typical of porphyria at this stage of the pregnancy According to Waldenstrom (1937) porphyric patients never show signs of œdema despite oliguria neither is proteinuria a common symptom in porphyria Hitherto there has been no report in the literature of late toxæmia of pregnancy occurring in a porphyric patient It seems likely however, that the patient whose case is described here suffered from two different pathological conditions, the symptoms of late toxæmia during the second half of pregnancy being superimposed on the symptoms of porphyria

sounds were normal Despite administration of Largactil and hypertonic glucose infusion, one eclamptic convulsion occurred, which was controlled by administration of Evipan and opiates Four hours later the patient was able to speak normally With an intravenous Puroverin drip during the first two days, Puroverin intramuscularly, and later occasional Largactil and Pethidine orally, it was possible to keep the blood pressure almost normal Laboratory tests Hgb 10 0 gr %, erythrocytes 3 360 cu mm, leucocytes 6 700 cu mm hæmatocrit 21, Meulengracht 1 6, rest-N 40 mg % alkali reserve 43 1 vol % CO_2, serum protein 6 7 per cent Proteinuria increased to 1 per mille Urine 250–1200 gr/day Although the period of gestation was only 33 weeks Cæsarean section was performed under epidural anæsthesia on April 9th because of the patient s relatively poor condition The infant, a live boy weighing 1,460 gr, was discharged from the Children s Hospital 6 weeks later in good condition After the Cæsarean section a Puroverin drip again had to be instituted from time to time to control the blood pressure Periods of restlessness alternated with calmer periods From April 16 on, the patient again complained of pains in the abdomen and back Urinary output after the Cæsarean section decreased from 1,500 cc/day to 250 cc/day within a week On April 20th the patient was moved to the Department for Internal Diseases[1] Neurological examination showed spasticity of the right arm and leg obviously due not only to the porphyria but to damage to the basal ganglia as a sequel of the eclamptic attack The porphobilinogen reaction remained strongly positive all the time but the general condition of the patient improved Her ability to speak increased, the muscular weakness decreased and mobility improved On May 29th however, the patient suddenly stopped speaking and expired within a few minutes At autopsy nothing pathological was found in the brain or spinal cord

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DETECTION OF PREDIABETES BY MODIFIED EXTON-ROSE GLUCOSE TOLERANCE TEST SENSITISED BY CORTISONE

BY

GUNNAR ENGLESON AND TOR LINDBERG

Investigations by, among others, Allen (1939), Miller (1946), Kriss and Futcher (1948), Paton (1948), Gilbert (1949), and Moss and Mulholland (1958) have demonstrated that women who give birth to infants weighing more than 10 pounds show a subsequent tendency to develop diabetes Further studies have indicated that in parturient women, the birth of a child weighing more than 4,500 g may itself constitute a prediabetic symptom Fitzgerald, Malins and O Sullivan (1961) performed gluco e tolerance tests on 61 wom n, who 13 years pre viously had given birth to infants weighing more than 4,500 g They found that 20 of these had definite or probable diabetes Pedersen (1961) detected overt or latent diabetes in 44 per cent of 182 women who had produced infants exceeding 4 500 g at birth 20 years previously Pirart (1955) maintains, however, that there is also correlation between obesity in the mother and high birthweight in the offspring

Hitherto such information has, as a rule been derived from retrograd studies and it is only in recent years that glucose tolerance testing during pregnancy or labour has been adopted to provide information concerning carbohydrate metabolism in the prediabetic woman Jackson (1952), Kritzer (1952), Lund

SUMMARY

A case of the rare occurrence of pregnancy and acute intermittent porphyria is described The diagnosis of porphyria was established several years before the first pregnancy This pregnancy was terminated because the already severe porphyria grew considerably worse during the first three months During the second pregnancy one and a half years later, the patient being now 27 years old, there were again repeated attacks of porphyria From about half way through the pregnancy symptoms of late toxæmia, with one episode of eclamptic convulsions, dominated the clinical picture Seven weeks before term a live infant weighing 1,460 gr was delivered by Cæsarean section, performed because of increasing symptoms of late toxæmia The condition of the patient improved remarkably during the weeks immediately after delivery Six weeks after the birth, however, the patient suddenly died At autopsy nothing pathological was found either in the brain or in the spinal cord

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cases Thus, 234 glucose tolerance tests were carried out during the puerperium and 155 were subsequently performed as out patient procedures

The Hagedorn Jensen method was used for blood sugar deter minations and the glucose-oxidase test for urinary sugar

Criteria employed in assessing glucose tolerance curves

The following were regarded as limits of the normal

For ordinary glucose tolerance determinations – less than 180 mg per 100 ml after one hour and less than 160 mg per 100 ml after two hours No glycosuria permitted

For cortisone glucose tolerance determinations – less than 220 mg per 100 ml after one hour and less than 180 mg per 100 ml after two hours Glycosuria permitted

Results

Control group

Ten women who had produced infants not exceeding 3,800 g at birth served as normal subjects during the puerperium Figure 1 shows the normal tolerance curve obtained by the methods described – GTT_A = without cortisone and GTT_B = with cor tisone

It should be pointed out that glycosuria appeared in 4 cases after determining glucose tolerance using cortisone (GTT_B)

Clinical material

An analysis of the clinical material is to be found in Tables I and II The family history was positive for diabetes in 23 cases the incidence being the same in the normal as in the abnormal cases There was no significant difference in the mean age Bodyweight was within normal limits in the majority of cases but patients with abnormal tolerance curves appeared rather more frequently in the 'heavyweight' class A number of patients were frankly obese but the investigation as a whole appeared to be little in-fluenced by obesity as such

and Weese (1953), Hoet (1954, 1956), Wilkerson (1959) and Hagbard (1958)

In 1954 Fajans and Conn introduced the cortisone glucose tolerance test as a diagnostic method in latent diabetes They utilized cortisone's diabetogenic effect in order to increase diagnostic accuracy, and were in this way able to demonstrate diminished glucose tolerance in the relatives of diabetics

This technique has since come into general use, either modified or in the original form, as a means of diagnosing the prediabetic state in women, Jackson (1961)

Since the early detection of diabetes is of the utmost importance we have attempted to attain greater precision in the diagnosis of prediabetes by using a modification of the Exton Rose technique combined with cortisone

Clinical material and methods

The series comprised 136 women, who were admitted to the Obstetrical Department, University Hospital, Lund, during the period 1956–1959 All had given birth to a living child weighing 4,500 g or more

Glucose tolerance tests were performed by the Exton Rose method (1934) and, in addition, a fourth blood sugar determination was carried out after 2 hours Glucose was given on a basis of 1 75 g per kilo bodyweight divided into two equal doses with an interval of half an hour *Cortisone-glucose tolerance tests* were carried out as described by Fajans and Conn (1954), so that the patients received two 50 mg doses of cortisone 8½ and 2 hours respectively before glucose was given Patients weighing over 80 kg were given 62 5 mg cortisone per dose

Determinations in the puerperium were carried out during the patients' stay in the maternity department, the first determination being as a rule on the fourth day and the second on the sixth day *post partum*

After discharge from hospital the subjects underwent subsequent glucose tolerance tests as outpatients, the first occasion being after an interval of a month and subsequently, if possible, every sixth month This shedule could not be adhered to in all

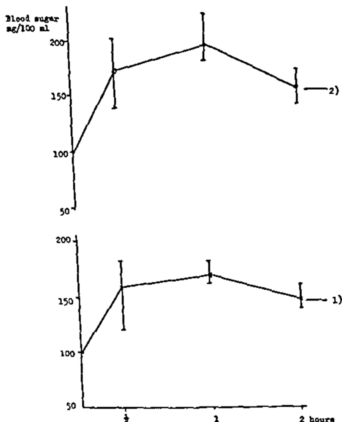


Fig 1 10 controls 1) GTT by modif Exton Rose 2) Cortisone-GTT by modif Exton Rose Vertical bars represent range

Glucose tolerance without cortisone-sensitization (GTT_A) was determined in 136 women Of these 22 were considered to have abnormal tolerance curves, figure 2

Determinations after administration of cortisone (GTT_B) were carried out in 98 patients and of these 32 were adjudged abnormal, figure 3

Eighteen of the 22 women with abnormal GTT_A curves were subjected to GTT_B The curves obtained were abnormal in all cases

Table 1 *Survey of Case Material*

	No of Cases	Heredity	Mean Age	Weight (kg)						Mean Weight
				40–59	60–69	70–79	80–89	90–99	100–120	
Normal GTT	93	15	29 7 yr (18–45)	19	31	29	9	4	1	74 kg
Pathological GTT	43	8	32 8 yr (21–43)	3	15	10	9	5	0	73 3 kg
Total	136	23	30 5 yr	22	46	39	18	9	1	73 7 kg

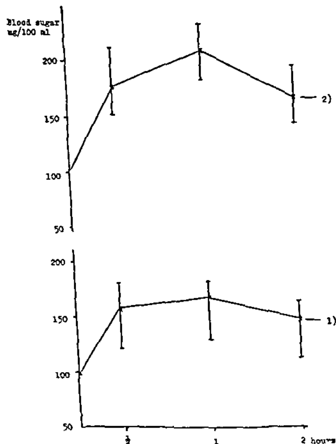


Fig 2 Case material GTT by modif Exton Rose 1) Normal GTT_A (114 cases) 2) Pathological GTT_A (22 cases) Vertical bars represent range

In a number of cases, however, an abnormal curve was first obtained at a later examination Thus, two abnormal curves were obtained for the first time at the second examination after discharge, one at the third and one at the fourth

A total of 43 patients exhibited an abnormal curve at one time or another (see Table I)

Manifest diabetes appeared in a total of 7 cases Of these, one had an abnormal curve at the first examination (GTT_A) and three

Table II *Parity in Relation to Glucose Tolerance Tests*

Parity	No of Cases		
	Pathol GTT	Normal GTT	Total
1	4	17	21
2	10	33	43
3	5	16	21
4	13	10	23
5	6	10	16
6	2	3	5
7	0	1	1
8	0	0	0
9	1	1	2
10	1	0	1
11	1	0	1

A course of tolbutamide was given to 13 of the 22 women with abnormal GTT_A curves The results of this will be described in a separate paper

Follow-up

Four weeks after discharge from the obstetrical department the patients were submitted to glucose tolerance determination with out cortisone (GTT_I) and the investigation was thereafter repeated at six-month intervals The duration of the follow up study varied from one month to five years as is apparent from Table III, and the number of tolerance tests involved is recorded in Table IV Table IV shows that 27 abnormal curves were obtained from 14 patients The majority of these abnormal curves were obtained soon after childbearing

Table III *Time of Observation Number of Cases*

		1 Month	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years
Total material	136	77	46	34	17	8	3	1
Normal GTT	93	45	23	16	7	2	0	0
Pathological GTT	43	32	23	18	10	6	3	1

Table IV GTT in the Puerperium (1) and at Follow up (2)

	No of GTT				Manifest Diabetes
	Normal GTT	Pathologic GTT (9+14 Cases)		Total	
		Pathol. at an Earlier GTT	Pathol. for the First Time		
GTT_A	114	0	22	136	1
GTT_B	66	18	14	98	3
$Total_1$	180	18	36	234	4
GTT_I	68	6	3	77	2
GTT_{II}	32	3	2	37	1
GTT_{III}	12	3	1	16	0
GTT_{IV}	7	2	1	10	0
GTT_V	4	3	0	7	0
GTT_{VI}	2	1	0	3	0
GTT_{VII}	2	0	0	2	0
GTT_{VIII}	1	0	0	1	0
GTT_{IX}	0	1	0	1	0
GTT_X	0	1	0	1	0
$Total_2$	128	20	7	155	3
$Total_{1+2}$	308	38	43	389	7

had abnormal GTT_B-curves (puerperal cortisone-glucose tolerance test) Two patients exhibited an abnormal GTT for the first time at GTT_I and one patient for the first time at GTT_{II} All underwent a period of treatment with diet and sulphonylurea derivates In no case was insulin required, but two patients needed continuous tolbutamide therapy

It is of interest to note that of the 66 patients with normal GTT_B seven developed an abnormal GTT later on Of these, two subsequently exhibited clinical signs of diabetes

Eight of the 23 women with a positive family history for diabetes (whose GTT_A and GTT_B curves are shown in Figure 4) showed abnormal curves – 4 being abnormal at examination GTT_A

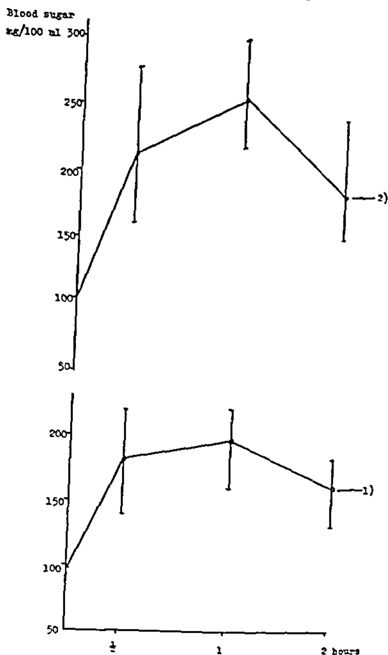


Fig 3 Case-material. Cortisone-GTT by modif Exton Rose 1) Normal cortisone-GTT (GTT_B) (66 cases) 2) Pathological cortisone-GTT (GTT_B) (32 cases) Vertical bars represent range

165 women including 33 who had given birth to infants exceeding 4 500 g Nine of these had diabetic or prediabetic type GTT curves an incidence approximating that observed by us Jackson (1952) found furthermore an abnormal GTT in 10 other patients who in one way or another had an abnormal obstetrical history (stillbirth toxaemia etc)

Lund and Weese (1953) described a series of 30 pregnant women who had previously produced infants exceeding 4 500 g Standard GTT was abnormal in 44 per cent as against 8 per cent in a control series of 60 pregnant women The authors asserted that the GTT usually returned to normal during puerperium If this did not happen the patient concerned was regarded as having unrecognized diabetes mellitus Such was the case in two of the patients

In 1958 Hagbard published details of a study similar to ours 189 women who had babies exceeding 4 500 g birthweight or who had had several pregnancies ending in intrauterine or neonatal deaths were submitted to a standard GTT during the puerperium 19 5 per cent were regarded as having an abnormal tolerance curve as against 4 per cent in a control series of 100 women whose children had weighed between 3 000 and 4 000 g at birth

Wilkerson (1959) published some results from a large scale serial study of pregnant women Among those who had earlier given birth to big babies (over 4 500 g) 13 5 per cent had an abnormal standard GTT Bertrand and Gilbert (1960) gave an account of a series comprising 60 women who had given birth to babies exceeding 4 500 g These patients were submitted to glucose tolerance tests with and without prednisone from 6 months to 15 years afterwards Two patients had an abnormal standard GTT while half of the series had abnormal prednisone GTTs It is to be emphasized however that in a contemporary control series of 45 women whose babies weighed less than 4 500 g at birth 31 per cent had an abnormal prednisone GTT

Fajans and Conn have since 1954 published a number of studies concerning prediabetes In one such published in 1961 the results were as follows The investigation consisted of an 8 years study of 393 healthy relatives of diabetic patients In 26 per cent a pathological cortisone GTT was obtained During the ob er

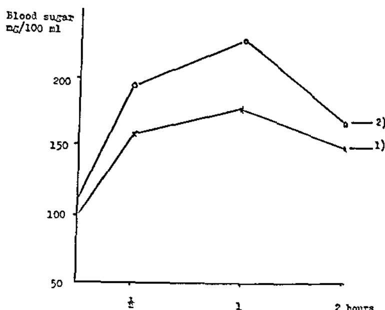


Fig 4 Patients with family history of diabetes GTT by modif Exton Rose
1) GTT_A (23 cases) 2) GTT_B (cortisone-GTT) (15 cases)

a further 3 at GTT_B and the 8th at the first examination after discharge Two patients in this group developed diabetes

To summarize, 43 (31 6 per cent) of the 136 women examined had at one time or another an abnormal GTT At examination GTT_A the incidence of abnormal results was 16 2 per cent Of the 98 women examined by cortisone glucose tolerance method, 32 (or 32 7 per cent) had abnormal tolerance curves Of 80 cases with a normal GTT_A, 14 (or 21 2 per cent) had an abnormal GTT_B

Discussion

The results of our investigation agree to a certain extent with those reported earlier in the literature

Thus Kritzer (1952) gives an account of a series of 58 women, who were studied 2½ years after giving birth to infants exceeding 5,000 g at birth The standard GTT was abnormal in 31 per cent Jackson's (1952) series from the same year comprised in all

infants all with birthweights of 4,500 g or thereabouts In these cases there would appear to be some connexion between parity and prediabetes, an observation which has been much debated previously, among others by Jackson (1961) who maintains that no significant relationship between these factors was found to exist in his series As Table II shows, we have analysed our cases from this viewpoint and pathological glucose tolerance curves appear rather more frequently with increasing parity This would suggest that repeated pregnancy can constitute a stimulus to the development of diabetes, a view which is held by many workers in this field (among others Hoet 1954) Our series is, however, too small to allow of hard and fast conclusions

As mentioned above an abnormal GTT_A was obtained in 22 cases In 13 of these a 10 day course of sulphonylurea was given At subsequent GTT_I all had normal curves except one and this, too returned to normal at GTT_{II} In no cases has manifest diabetes so far appeared It is probable that tolbutamide has had a favourable effect on the prediabetic state in these cases, and that a number of them would have developed diabetes if sulphonylurea not had been given In the nine untreated patients clinical diabetes appeared in one

Cortisone glucose tolerance (GTT_B) was tested in 98 cases and pathological curves were obtained in 32 Eighteen of these 32 also had an abnormal GTT_A Of the remaining 14, three have since developed diabetes Manifest diabetes has appeared in 2 cases of the 66 who had normal cortisone glucose tolerance tests

An important question in this study is whether or not cortisone-GTT represents an improvement in the methods for detecting prediabetes On this point opinions vary Fajans and Conn (1961) Duncan (1956) West (1957) and Goto *et al* (1960) regard cortisone or prednisolone GTT as being of great value, while Goudie *et al* (1958) who investigated asymptomatic glycosuria by means of tolerance testing, and German (1958) who carried out tolerance tests on normal and obese subjects were unable to detect any difference in comparison with standard GTT Bertrand and Gilbert (1960) had, as mentioned previously observed a pathological prednisone GTT in 31 per cent of their control series Jackson (1961) maintains that with cortisone

vation period it was found that of those who reacted positively at the first cortisone-GTT, 26 per cent developed diabetes and a further 9 per cent probable diabetes Of those cases with an initial negative reaction, 3 per cent developed clinical diabetes

Goto and co-workers (1960) published the results of an investigation comprising 17 relatives of diabetics, who were submitted to prednisolone-glucose tolerance test In 35 per cent a diabetic curve was obtained

In our series 43 of 136 patients, that is to say 31 6 per cent had a pathological tolerance curve at one time or another In 22 instances (16 2 per cent) GTT_A was abnormal, and in 32 instances (32 7 per cent) GTT_B (puerperal cortisone-glucose tolerance test) was abnormal Before attempting to assess these results it should be emphasized that the observation period has so far been relatively short Opinion is divided as to how soon a prediabetic woman will develop manifest diabetes, but an interval of at least 5 years is the generally accepted view For this reason our results can not yet be regarded as final, and the investigation is not yet concluded It is thus very probable that manifest diabetes will later appear in further cases in this series Having regard to the short observation period, the number of cases of manifest diabetes which have so far appeared is relatively large

Closer analysis of these seven cases of diabetes should be of interest Only one patient had a pathological first tolerance test (GTT_A) This 27-year old woman had no family history of diabetes, was of normal bodyweight and was para-IV Not only had her most recent baby a high birthweight, but 2 earlier babies born 3 and 2 years previously, respectively, both weighed more than 4000 g Three patients had pathological cortisone glucose tolerance curves, and of these, two had a family history of diabetes Fajans and Conn (1954) among others, have reported that the incidence of pathological cortisone-glucose tolerance curves is greater among those with a positive family history Of the remaining three patients who showed abnormal tolerance curves at later examinations, one had a strongly positive family history and 3 previous infants with birthweights of from 4,500 g to 5,100 g One patient had 2 previous infants with birthweights around 4,500 g, one of which died in the neonatal period The third patient had 3 earlier

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GTT there can appear both false negative (normal cortisone GTT in patients with obvious diabetes) and false positive results (during pregnancy and in older age) This view is shared by Fajans *et al* (1961), who considers that cortisone GTT is valueless during pregnancy since too many positive results are obtained Jackson (1961) points out that cortisone-GTT is difficult to interpret and does not recommend its routine use Luft (1961) is of the same opinion, regarding cortisone-GTT as of doubtful value

In this study, cortisone-GTT has proved of less value than we had originally hoped It would appear that there is a tendency towards abnormal cortisone-GTT even when the test is carried out in the puerperium, rather than during pregnancy when according to, among others Hoet (1954, 1956), the diabetogenic effect of pregnancy should have disappeared How rapidly the 'diabetogenic effect of pregnancy disappears is difficult to determine but it probably does so during the puerperium Since, in our series, *tolerance testing was carried out in the puerperium*, positive results were less likely to occur than if the patients had been tested during pregnancy It can be maintained therefore that the results, as such, provide more information about the patients carbohydrate metabolism than if the investigations had been performed during pregnancy

It has proved difficult to fix normal limits for cortisone GTT A number of cases had one-hour values of 200–220 mg/100 ml *Values of over 220 mg/100 ml, however, as occurred in 32 cases* must be regarded as clearly pathological Cortisone GTT proved unreliable in the seven patients who had manifest diabetes normal curves being obtained *in two cases*

The cortisone-glucose tolerance test can not be pronounced as unsatisfactory until a longer observation period has elapsed Probably, however, GTT without cortisone is to be preferred during or after pregnancy

Of our seven cases with manifest diabetes only two required continuous oral treatment with sulphonylurea The remaining five were rendered symptom free by means of diet and weight reduction Since, as a rule, relatively young patients are involved it is regarded as of great value that the disease can thus be detected at an early stage when treatment presents no great problem For

this reason we are anxious to stress the merits of this type of investigation for diagnosis of prediabetes

As regards hereditary factors, in 8 of the 23 patients with a positive family history an abnormal GTT was obtained This is a high figure Four of the cases gave abnormal results at the first tolerance determination, while a further three registered a pathological GTT_B This supports the findings of other workers, namely that the cortisone glucose tolerance is often abnormal in relatives of diabetics Two of these cases developed frank diabetes, one being a IV para

To *summarise* the investigation the following can be said The birth of an infant weighing more than 4 500 g may constitute a sign of maternal prediabetes, since there appears to be a consider able risk that diabetes will develop subsequently This risk is increased by further such pregnancies, and is considerably in creased if there is also a family history of diabetes In any individual patient obesity will further increase such risk Due to the relatively short observation period reliable incidence figures can not be arrived at

The results obtained suggest that manifest diabetes can develop quite soon after the detection of prediabetes in the individual patient

Of cortisone glucose tolerance testing, it can be said that even in the puerperium, there is difficulty in determining normal limits

For this reason, GTT without cortisone or prednisolone would seem preferable The modified Exton Rose method is in our view the method of choice for this type of work, and its use is recom mended for the detection of prediabetes in patients giving birth to heavy babies

SUMMARY

During the period 1956–1959 investigations aimed at detecting the presence of prediabetes were carried out on 136 women who had given birth to infants exceeding 4 500 g

Glucose tolerance tests (GTT) were performed during the puerperium using a modification of the Exton Rose method some times using cortisone and sometimes not Subsequently, GTTs

GTT there can appear both false negative (normal cortisone GTT in patients with obvious diabetes) and false positive results (during pregnancy and in older age) This view is shared by Fajans et al (1961), who considers that cortisone-GTT is valueless during pregnancy since too many positive results are obtained Jackson (1961) points out that cortisone-GTT is difficult to interpret and does not recommend its routine use Luft (1961) is of the same opinion, regarding cortisone-GTT as of doubtful value

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It has proved difficult to fix normal limits for cortisone GTT A number of cases had one hour values of 200–220 mg/100 ml Values of over 220 mg/100 ml, however, as occurred in 32 cases must be regarded as clearly pathological Cortisone GTT proved unreliable in the seven patients who had manifest diabetes, normal curves being obtained in two cases

The cortisone-glucose tolerance test can not be pronounced as unsatisfactory until a longer observation period has elapsed Probably, however, GTT without cortisone is to be preferred during or after pregnancy

Of our seven cases with manifest diabetes only two required continuous oral treatment with sulphonylurea The remaining five were rendered symptom free by means of diet and weight reduction Since, as a rule, relatively young patients are involved it is regarded as of great value that the disease can thus be detected at an early stage when treatment presents no great problem For

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without cortisone were performed at six-month intervals The longest observation time so far is five years Altogether, 389 glucose tolerance tests have been carried out

In all, 43 patients were found to have pathological glucose tolerance curves In 22 cases the curve was abnormal at the first examination, in further 14 cases at the second examination (with cortisone), and in the remaining seven cases the curve became abnormal on a subsequent occasion

Manifest diabetes appeared in a total of 7 cases, despite the short observation period Of these 2 required continuous tolbutamide therapy

The study has shown that the birth of a heavy baby can be a sign of prediabetes in the mother, with the risk of subsequent manifest diabetes A family history of diabetes, the birth of further heavy babies and obesity increase this risk in the individual patient

The use of cortisone-GTT involves the same difficulties in the puerperium as it does during pregnancy with regard to evaluation of the resulting bloodsugar curves In the present investigation the use of a modified Exton-Rose method appeared to represent an advance in diagnostic precision

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abnormal glucose tolerance curves were given sulphonyl urea and our findings in these cases constitute the subject matter of the present paper

Clinical Material and Methods

The clinical material consisted of 22 women who were selected from a series of 136 patients studied at the Obstetrical Clinic, Lund, over the period 1956–1959, and of which an account is given in the earlier article (Engleson and Lindberg, 1962) These women were delivered of living babies weighing 4 500 g or more at birth

Glucose tolerance tests (GTT) were performed using a modification of the Exton Rose (1934) method with a fourth blood sugar estimation after 2 hours 1 75 g glucose was given per kg bodyweight divided into two doses with half an hour interval Cortisone glucose tolerance was tested by the method of Fajans and Conn (1954) The patients were given 50 mg cortisone 8½ and 2 hours respectively before beginning the tolerance test Patients weighing more than 80 kg were given 62 5 mg of cortisone

One tolerance test without and one with cortisone were performed on the fourth and sixth days *post partum* Glucose tolerance without cortisone was tested in all 22 patients and with cortisone in 18 patients

Blood sugar (Capillary blood) was determined by the Hagedorn Jensen method and urinary glucose by the glucose oxidase method

All 22 patients had abnormal GTTs during the puerperium Fig 1 shows this curve in contrast to the normal curve of the remaining 114 women in the series

Thirteen patients were given a 10-day course of tolbutamide after cortisone glucose tolerance testing Each was given a total of 12 g tolbutamide (Rastinon tablets) according to the following dosage scheme

1st day 3 g
2nd + 3rd day 2 g per day
4th day 1 5 g

Engleson Gunnar Lehmann Orla and Lindberg Tor Acta obst et gynec scandinav 41 339 1962

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SULPHONYLUREA-TREATMENT IN PREDIABETIC WOMEN

BY

GUNNAR ENGLESON ORLA LEHMANN AND TOR LINDBERG

In recent years the early diagnosis of diabetes has aroused increasing interest By means of so-called diabetes detection drives" (Wilkerson *et al*, 1947, Kenny *et al*, 1951, Schersten, 1960) cases have been brought to light while still in the asymptomatic stage Investigations have furthermore disclosed that women giving birth to unusually heavy babies show an increased incidence of frank diabetes subsequently

This early detection of diabetes in the latent stage renders prophylactic treatment feasible, and the use of sulphonylurea for this purpose has been widely discussed The work of Loubatiere (1946) demonstrated that sulphonylurea derivatives act by stimulating insulin production in the beta-cells of the pancreatic islets Loubatiere (1960, 1961) also suggested the use of these derivatives as a prophylactic measure in various forms of latent diabetes Studies along these lines have been carried out by Fajans and Conn (1960)

Engleson & Lindberg (1962) have previously published the results of a study carried out on a series of women who had given birth to infants weighing over 4,500 g These women were subjected to repeated glucose tolerance tests aimed at revealing the possible presence of latent diabetes

In the course of the above study, a number of patients with

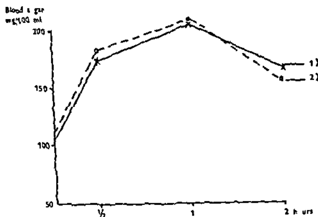


Fig 2 GTT after modif Exton Rose 1) Group I (13 cases) 2) Group II (9 cases)

were submitted to cortisone glucose tolerance testing the resulting curves being abnormal in all

These two groups were uniform as regards diabetic heredity background mean age, average weight and parity

Follow up Studies

Sixteen patients were submitted to a third glucose tolerance test, without cortisone one month after discharge from hospital 11 from group I and 5 from group II A number of patients subsequently underwent testing usually at 6 month intervals The longest follow-up period was five years

The patients present state of health 2–5 years after childbirth was asses ed by mean of a questionaire which was sent to those concerned Urine sugar examinations (Clinistix) were carried out at the same time

Results

The glucose and cortisone glucose tolerance curves obtained from both groups during the puerperium can be seen in Figs 2 and 3 All are abnormal and no difference between the two groups can be seen

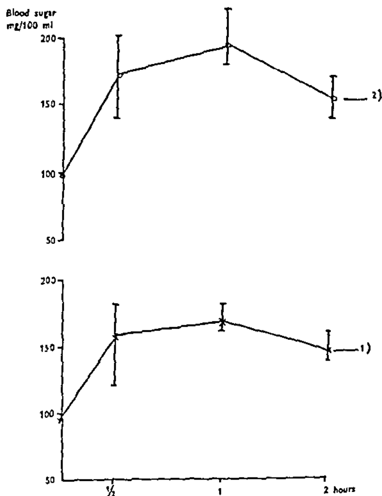


Fig 1 Clinical material GTT after modif Exton Rose 1) Normal GTT (114 cases) 2) Pathological GTT (22 cases) Vertical bars represent range

5th + 6th day 1 g per day
7th to 10th day ½ g per day

The series can be divided into 2 groups

Group I Thirteen patients with abnormal glucose- and cortisone glucose tolerance curves who were subjected to the aforementioned treatment as well as a degree of dietary control

Group II Nine patients, all with abnormal glucose tolerance curves who received no sulphonylurea Five of these patients

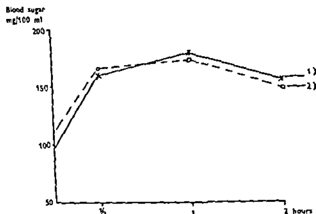


Fig 4 GTT after modif Exton Rose

Group I (11 cases) 1 month after tolbutamide therapy
Group II (5 cases) without tolbutamide therapy

Group II In 5 patients submitted to a third glucose tolerance test, a pathological curve was obtained in one A fourth GTT was done in 3 cases two of these being normal The third patient (whose 3rd GTT was also abnormal) underwent three further tests during the ensuing 4 – year observation period the curve being abnormal on each occasion This patient developed frank diabetes requiring diet and tolbutamide treatment

Enquiries (from 7 patients) subsequently revealed the following One patient developed overt diabetes The remaining six showed no sign of diabetes up to the end of the five year observation period None had glycosuria One woman (para VI with a history of one previous infant weighing over 4 500 g at birth) had a further child with a birthweight of 4,000 g

The third GTT in both groups is shown in fig 4 No differences can be observed

Discussion

During the relatively short observation period (maximum 5 years) which has so far elapsed it can be seen that the two groups

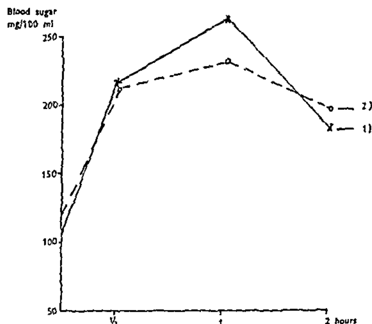


Fig 3 Cortisone-GTT after modif Exton Rose 1) Group I (13 cases) 2) Group II (5 cases)

Follow-up

Group I Eleven of the 13 patients were subjected to a third glucose tolerance determination One of these patients had an abnormal curve Six months later the glucose tolerance curve was normal in the same patient Five patients were subjected to a fourth determination, all being normal One patient was subjected to a fifth determination, and this, too, was normal

The follow-up enquiries by questionaire (to which 12 patients replied) gave the following results None developed manifest diabetes during the course of the 3½ year observation period In the eleven patients examined, no glucosuria could be demonstrated Two of the patients gave birth to further children One of these babies weighed 4,600 g the mother being a VI para whose previous obstetric history included the birth of two babies weighing over 4,500 g The other baby weighed only 3,900 g at birth, while the mother, a IV-para, had 3 times previously been delivered of babies weighing 4,500 g or more

gramme in these subjectively well patients Further study will, no doubt, point the way to the most satisfactory method

Conclusions

Having regard to the limited scope of the study and the inadequate duration of the follow up period, the writers refrain from drawing any hard and fast conclusions as to the value of prophylactic tolbutamide therapy in the prediabetic state Theoretically, such treatment is well justified but only further study will reveal whether it is rewarding in practice

SUMMARY

During the period 1956–1961, an attempt was made to assess the value of prophylactic tolbutamide therapy in 22 prediabetic women 13 of these patients received a total dose of 12 g tolbutamide each over a 10 day period while 9 patients acted as controls During the follow up period, none of the treated patients developed diabetes In the control series one patient developed manifest diabetes during the same period This difference is not statistically significant but theoretical considerations would seem to justify continued investigation

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differ in so much as that *one* untreated woman has developed overt diabetes as against none in the treated group

This difference is not statistically significant Comparison of the third GTTs, one group with the other, reveals no differences It is thus impossible to conclude whether or not the tolbutamide treatment had any certain effect It should be pointed out, however, that only five of the nine cases in Group II were submitted to a third tolerance test

It can be said that of the nine women in Group II, only one developed diabetes in the subsequent five years, wich emphasises the difficulty in forecasting the development of manifest diabetes in untreated prediabetics This naturally influences any attempt to assess the value of prohylactic tolbutamide therapy That manifest diabetes can, however, appear shortly after the detection of a prediabetic state has been demonstrated by a previous investigation (Engleson and Lindberg, 1962)

Further study is obviously required before the value of a single course of tolbutamide treatment can be accurately determined

Few reports on prophylactic tolbutamide treatment have hitherto appeared and there is no general agreement on how this treatment is best carried out Fajans and Conn (1960) prescribed 1 g tolbutamide daily for considerable periods, up to 27 months They noted that improvement in the glucose tolerance curve appeared in certain cases only after several months treatment

We consider, however, that the method herein described, namely a 10 day course, repeated if necessary, is more generally suitable *Earlier experience with sulphonylurea derivatives* in the treatment of juvenile diabetes in the post-initial phase (Engleson and Lehmann, 1957, 1959) suggests that a 10 day course of tolbutamide is sufficient to attain increased production of endogenous insulin Furthermore, tolbutamide has not been without effect in the present series, since the glucose tolerance curve afterwards reverted to normal in all cases

Further, it is possible that prolonged sulphonylurea treatment could lead to beta cell exhaustion, a point which mitigates against continous therapy There would also seem to be practical difficulties involved in carrying through a long term treatment pro

Several of the above mentioned series include varying numbers of premature deliveries, but no attempts have been made to analyse the special factors which apply in these cases

Roth (1954) submitted a series of 54 cases with rupture of the membranes prior to the 38th week of gestation The maximum latent period was 26 days, and in about 40 per cent labour ensued within 50 hours The perinatal mortality was a little over 20 per cent In comments on this study Eastman (1955) reported his experience on a total of 540 cases of premature rupture of the membranes (birth weights 1,000–2,499 g) In 51 per cent the latent period was less than 24 hours, in 69 per cent less than 48 hours and in 80 per cent less than 72 hours Moreover, the latent period increased with the degree of prematurity In another series of Eastman s (not published) the mortality of mature infants rose with increasing latent period while in prematures it was the prematurity as such which caused the high mortality The maternal morbidity was in no way appreciable and could be further reduced by antibiotic therapy during the latent period

In 1961 Breese published a series of 515 cases of premature rupture of the membranes (birth weights 501–2 500 g) corresponding to 1 per cent of all deliveries in the hospital concerned Of these infants 60 per cent were in the weight group 2,001–2 500 g and the total perinatal mortality was 30 9 per cent The maternal morbidity (7 8 per cent) was approximately 3 times the average in the department, while the maternal mortality was 0 Compared with all prematures of the same weight groups the infant mortality following premature rupture of the membranes was somewhat higher (19 2 per cent) in the group 1,501–2 500 g as compared with 15 1 per cent among all prematures, while in the group 501–1,500 g it was a little lower The latent period was less than 48 hours in 50 7 per cent and increased with the degree of prematurity If the latent period exceeded 48 hours the infant mortality was higher in all weight groups especially in the 2 001–2 500 g group in which it was doubled There was only a slight increase in maternal morbidity at latent periods exceeding 48 hours (7 3 to 8 3 per cent) but antibiotics were used more often in cases with long latent periods A total of 27 6 per cent were breech deliveries with an infant mortality which

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PREMATURE RUPTURE OF THE MEMBRANES AT FŒTAL WEIGHTS OF 1,000—2,500 G

BY

BJORN BUEMANN AND PER LANGE

Premature rupture of the membranes about or shortly before term has previously been studied in detail, but premature rupture at an earlier stage of pregnancy has received little attention Since, however, no small proportion of premature deliveries start with *rupture of the membranes, we felt it would be of interest to* analyse a group of such patients, especially in respect to the value and risks of expectant management

It is generally agreed that after premature rupture of the membranes around term, labour sets in spontaneously within 24–48 hours in 70–90 per cent of the cases (Biskin and Biskin, 1957, Cron and Brown, 1953, Ekvall *et al*, 1961, Embrey, 1953, Lebherz *et al*, 1961, Morton *et al*, 1942, Schulze, 1929) Several authors have demonstrated an increasing infant mortality with increasing latent period (i e the period from rupture to start of labour) (Embrey, Lebherz *et al* Morton *et al*), while the increase in infant morbidity is slight and the maternal mortality very low *Furthermore, it has been shown by several* authors Bainbridge *et al*, 1958, Calkins, 1952, Essen-Moller, 1936, Fredrikson, 1937, Sunde, 1937) that the first stage of labour is shorter if the membranes rupture early, so that such an onset of labour would not appear to be unfavourable in all respects

Aided by a grant from the Vera and Carl Johan Michaelsen Foundation

the period 1955–1959 incl, a total of 326 cases All cases with an estimated fœtal wieght of between 1,000 and 2,500 were included, the selection thus being based on weight regardless of gestational age *A priori* all cases of twins were excluded, since in these cases special factors apply We interpreted premature rupture of the membranes as cases in which the passage of amniotic fluid preceded uterine contractions by at least one hour

Table I *Composition of the Series*

	1955	1956	1957	1958	1959	Total
Number of deliveries	2 179	2 373	2 359	2,428	2 384	11 723
Infants < 2 500 g	301	339	332	299	284	1 555
Infants < 2 500 g with premature rupture of the membranes	84	56	65	59	62	326

The high incidence of prematurity is due to the concentration of these cases at Rigshospitalet and does not reflect the incidence in Copenhagen On the other hand the fact that approximatively 20 per cent of the premature deliveries started with rupture of the membranes is more real, although in this respect too there is probably a slight preponderance at Rigshospitalet

Table II *Maternal Morbidity and Maternal Mortality*

	No of Cases	
Puerperal infection	5	1 5
Fever before and/or during parturition	27	8 2
Deaths	1	0 3

Table II shows a marked increase in the incidence of infection which was about 3 5 per cent among all cases admitted to the department during the period concerned Puerperal infection is defined as all cases having a temperature of 38° C or over beyond the evening of the first day, i e both cases of so-called one day fever and puerperal fever Fever before and/or during parturition comprises all patients having a temperature of 36° C or above during the latent period or during delivery

was, weight group by weight group, almost twice as high as that with cephalic presentation

Present Investigations

At the Maternity Department B, Rigshospitalet, Copenhagen, it has been a principle in cases of premature rupture of the mem branes to try to prevent the onset of labour when the fœtal weight was estimated between approximately 1,000 and 2,500 g At fœtal weights of less than 1,000 g the likelihood of a reasonable chance of survival was considered so slight that the mother should not be exposed to unnecessary risk In these cases, therefore, labour was induced In the weight group above 2,500 g it was not felt that the labour need be arrested

It may be difficult to make a precise diagnosis of ruptured membranes We have been content with the purely clinical diagnosis of a passage of fluid of characteristic odour by the vagina In rare cases the presumed amniotic fluid was collected for microscopic examination for lanugo hairs (Langreder, 1958), but pH determination, fat analysis, and crystallization test (Lang reder, 1958, Ruck, 1959, Krieger, 1957, Holbein and Heidingsfelder, 1960) were not performed

Our therapeutic regime is bed rest after admission with a sterile pad covering the genitalia Twenty four hours after the rupture of the membranes penicillin therapy is started, 200,000 units twice daily for 3 days It is then discontinued but is resumed in the event of uterine contractions If labour ensues, an attempt is made to inhibit it by opium suppositories, 100 mg up to several times daily and or/tetrapone (a morphine derivative) 1 ml, if necessary Progestogens have been used several times, but not routinely At the slightest sign of infection antibiotics are administered in large doses and labour is induced The delivery proper is conducted in the same gentle way as premature deliveries in general

Material

We analysed the cases of premature rupture of the membranes at an early stage of pregnancy in the Maternity Department B from

Table III *Birth Weight and Perinatal Mortality*

	No of Cases	Perinatal Deaths	% Deaths	Perinatal Mortality among All Prematures in Mat. Dept. B during the Same Period (in %)
< 1 000 g	1	1		
1 000–1,450 g	82	54	65 9	72
1 500–1 950 g	88	28	29 8	35
2 000–2,450 g	144	11	7 7	13
≧ 2 500 g	11	0	0	
Total	326	94	28 8	

There was one infant under 1,000 g and there were 11 over 2,500 g The infant who was less than 1 000 g had been estimated on admission as being of a greater weight and the case had been managed accordingly All 11 infants weighing more than 2,500 g had been estimated as being smaller on admission, and the majority were no doubt less than 2 500 g Table III shows that the distribution is shifted towards the lower weight groups as compared with prematures in Copenhagen as a whole in which the 2,000–2 500 g group makes up about 66 per cent (Kærn, 1959) against less than half in our series The perinatal mortality was only slightly higher than might be expected according to the birth weight (Kærn)

It is striking that the perinatal mortality was lower in cases of primary rupture of the membranes than among the prematures of the corresponding weight groups as a whole This is difficult to explain Part of the explanation may be that most cases of vaginal bleeding especially abruptio placentæ, with its consequent high infant mortality, fall outside our group of premature cases, and the same applies to some extent to the group of patients with toxæmia Moreover only 37 per cent of the patients were primiparæ and only 22 per cent unmarried, which is a somewhat more favourable social distribution than among the ordinary population of the department Furthermore most deliveries in the present analysis took place after due preparation in the department while a number of other premature infants are admitted after precipitate delivery at home

The infections did not cause direct complications of any severity except in one case (*vide infra*) Only 2 patients had fever for more than 3 days, and it was only in 6 cases that the temperature exceeded 39° C In other words, the infections were on the whole mild On the other hand there was one maternal death which is briefly described below

Case rec. 2490/57 A 22 year old Para III Admitted a few hours after rupture of the membranes in her home Estimated fœtal weight on admission 1,400–1,600 g The diagnosis of ruptured membranes was definite After 7 days in hospital, the patient became hyperpyrexial and was then treated with *penicillin in millon unit doses* Within 24 hours the patient went into labour and was delivered spontaneously A tense membrane which protruded from the orifice was punctured and yielded foul smelling amniotic fluid. The infant, in cephalic presentation, was stillborn, weight 1,700 g, length 44 cm A few hours after delivery the patient became shocked but improved temporarily with transfusion therapy Following a relapse signs of diffuse peritonitis appeared, and exploratory laparotomy was performed This revealed diffuse peritonitis, but no focus of infection Post operatively the patient was treated with blood transfusions, antibiotics, adrenocortical steroids, noradrenaline, and hypothermia, but despite this intensive therapy she died a little more than 24 hours *post partum* Autopsy under sterile conditions revealed sepsis due to E. Coli

Like others before us, we are able to offer little comment on the cause of premature rupture of the membranes, but the patients histories had not been taken with a special view to clarifying this aspect In a total of 8 there was a history of trauma during the days immediately preceding the event Two patients had been subjected to amputation of the cervix uteri and three to vaginal repair because of procidentia, and one had been treated for atresia uteri That is, in less than ½ per cent was there a reasonable eliciting cause To these may be added 14 cases of severe fœtal malformations which is, incidentally, a very high incidence A total of 128 patients (39 3 per cent) had a history of previous abortion or premature delivery During the period in question patients in this category had not been examined particularly for isthmus insufficiency The percentage of primiparæ was 37 2 per cent (122 patients) as compared with the normal 49 per cent in Department B, and 37 2 per cent were 30 years of age or over, which is somewhat higher than the normal average in the Copenhagen population (24 per cent)

Since the birth weight in the various groups is very much the same, this table also confirms that the latent period increases with the degree of prematurity The latent period ranged from 8 days to 4 5 months (135 days), averaging 3 weeks, and thus there was an average fœtal weight gain of 600 g It is difficult to assess the role of management No attempt was made to arrest the labour in 52 out of the 108 cases mainly because after having spent a long time in their homes following rupture of the membranes, the patients were admitted with such severe uterine contractions that any attempt at stopping them was useless In 56 cases an attempt was made to stop labour by opium suppositories and/or Tetrapone (a morphine derivative) In 15 this treatment was ineffective, and labour proceeded but in 41 cases the contractions ceased, and delivery was deferred for varying lengths of time The maternal morbidity in the group with a latent period exceeding one week showed a slight preponderance compared with the total series there being 11 per cent infections (puerperal 1 8 per cent – before and during parturition 9 2 per cent)

Table VI shows the perinatal mortality in relation to the latent period

Table VI *Perinatal Mortality in Relation to Latent Period*

	No of Cases	Perinatal Deaths	Expected Mortality According to Weight (in)	
< 24 hours	59	11	19	20
24–48 hours	76	22	29	22
2–7 days	83	21	25	27
> 7 days	108	40	37	32

At first sight it might appear that the perinatal mortality increased with an increasing latent period But if the mortality is corrected according to the birth weight in the various groups there is hardly any real increase with the latent period This is in accordance with the findings of Eastman (1955), but in conflict with Breese (1961) who found that the perinatal mortality doubled when the latent period exceeded 48 hours

As might be expected in a series of this nature there was a

Table IV *Latent Period and Average Birth Weight*

	No of Cases	%	Average Birth Weight
< 24 hours	59	18	2,050 g
24–48 hours	76	23 (18 + 23 = 41)	1 900 g
2–7 days	83	26 (18 + 23 + 26 = 67)	1,800 g
> 7 days	108	33	1,800 g
Total	326	100	

The latent period is taken to mean the interval from the rupture of the membranes until the onset of uterine contractions resulting in delivery Table IV presents several interesting facts Forty-one per cent of the patients went into labour within 48 hours, which is a considerably smaller proportion than is found in primary rupture of the membranes at term In was only in about one third that the delivery could be postponed for more than a week, and with a latent period of less than a week the increase in fœtal weight was negligible In the last column of Table IV the weights are approximately equal in the different groups, and this seems to indicate that, when the fœtus has attained a size approaching 2,000 g, labour will ensue, so that it would not appear to serve much purpose to try to arrest labour in the weight group exceeding 2,000 g We, therefore, quite agree with Eastman (1955) that the latent period increases with the degree of prematurity and thus gives a greater chance of fœtal weight increase the smaller the fœtal size

Further analysis of the 108 cases with a latent period exceeding one week is shown in Table V

Table V *108 Cases with a Latent Period Exceeding One Week*

	No of Cases	Average Duration	Average Birth Weight	Calculated Weight Gain
1–2 weeks	46	10 days	1 650 g	about 300 g
2–3 weeks	26	16 days	1 800 g	about 400 g
3–4 weeks	13	23 days	1,750 g	about 600 g
>4 weeks	23	46 days	1,900 g	about 1 000 g

SUMMARY AND CONCLUSION

From an analysis of 326 cases of premature rupture of the membranes at fœtal weights of 1,000–2,500 g seen during the years 1955–1959 inclusively, the following may be deduced

1 Primary rupture of the membranes occurs in approximately 20 per cent of all premature deliveries
2 The maternal morbidity is definitely increased In general, the complications are not serious, but they involve the possibility of an increased maternal mortality
3 The latent period increases with the degree of prematurity
4 Only in about 33 per cent does the latent period exceed one week
5 The perinatal mortality depends only to a slight extent upon the latent period, but is determined primarily by the degree of prematurity
6 In about 33 per cent of all cases expectant management can reduce the perinatal infant mortality by more than 50 per cent

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high incidence of breech presentations (18 4 per cent) and oblique presentations (3 1 per cent) The mortality among the breech presentations was 52 per cent (expected mortality according to weight groups 42 per cent) and that among the oblique presentations 40 per cent (expected 35 per cent), but the numbers in the latter group are probably too small to permit conclusions

Discussion

Patients with primary rupture of the membranes often put the obstetrician into a dilemma The fear of maternal infection tempts to rapid induction, while the risk of a greatly premature infant with little chances of surviving indicates expectant treatment Our maternal deaths of course made us uneasy, but judging by the literature, such deaths appear to be rare However, Ingerslev and Trolle have observed one case each in other obstetrical units within the past year The other infections in our cases were mild and did not give rise to much trouble As a matter of fact, nature will help disperse our doubts, as labour will ensue spontaneously within 24 hours in 40 per cent of the cases At an estimated fœtal weight of about 2,000 g there does not seem to be any reason to try to arrest labour, as the likelihood of success is slight and the infant's chances of surviving are fairly good With increasing degrees of prematurity the likelihood of successful expectant management increased without this apparently leading to higher infant mortality, despite the long-continued leakage which one might fear would result in fœtal infection

In the present series the result of expectant management was that in 33 per cent of the cases an average weight increase of about 600 g was obtained Thereby the perinatal mortality in this group was reduced from about 65 per cent to about 25 per cent On the other hand, there was one maternal death We feel that our results justify a continuation of the management used so far, with the only modification that no attempt should be made at arresting labour if the estimated fœtal weight exceeds 2,000 g

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FERTILITY, PREGNANCY AND LABOUR IN WOMEN WITH A HISTORY OF NEPHRITIS OR PYELONEPHRITIS

BY

LAURI RAURAMO ANTERO KASANEN KAARLE ELFVING AND HEIKKI SALMI

The connection between late toxæmia of pregnancy and renal disease is a subject of considerable interest. Many investigators have suggested that the incidence of organic kidney disease after pre-eclampsia is hardly greater than that in a normal population (see Rauramo, Kasanen, Castren, and Salmi 1959). On the other hand, Pollak and Kark (1961), who did kidney biopsies found that in 8 of 35 patients with histological evidence of pre-eclamptic glomerular lesions there was also histological evidence of underlying arteriosclerosis and hypertensive vascular disease. These lesions persisted after delivery.

Generally renal diseases manifested before and during pregnancy are meticulously recorded in obstetric case histories. For cases of acute nephritis occurring during pregnancy a maternal mortality rate of 33 per cent was reported by Wegner (1937). Abortion, premature labour and intrauterine death of the fœtus are all common. The obliterative changes in the vessels supplying the placenta begin earlier than normally. Fœtal mortality has been as high as 47 per cent (Corwin & Herrick 1927). In women with chronic glomerular nephritis, fertility is impaired and the pregnancy often ends in abortion. Pyelonephritis at the time of

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Table I *Number of Children in the Different Groups*

Number of Children	0	1	2	3	>3	Total
Nephritis	48	29	26	9	2	114
Pyelonephritis	147	105	86	29	16	383
Total	195	134	112	38	18	497[1]

[1] an additional 14 women had histories of abortion but no deliveries

Mortality

During the observation period, 28 patients died, 18 (15 2 per cent) in the nephritis and 10 (2 5 per cent) in the pyelonephritis group All except 5 died of chronic nephropathy and uræmia Two died of cerebral hæmorrhage, which can be regarded as a consequence of kidney disease One died of periarteritis nodo a confirmed by autopsy and apparently triggered off by the patient s nephritis One committed suicide One patient died at the time of delivery, due to afibrinogenæmia

Of the 195 nulliparous patients 8 of the pyelonephritis group and 14 of the nephritis group died The mortality was considerably lower among parous women *viz* 2 in the pyelonephritis and only 4 in the nephritis group *The apparently favourable prognosis in the parous category presumably follows from the low conception rate in women with the most serious conditions*

Effect of Age at Onset of Disease on Parity and Mortality

Table II gives the correlation between age at onset of the disease, and parity as well as mortality The table shows that none of the patients who fell ill when under 15 years of age died, but the number of patients in this group is too small to permit safe conclusions Table III gives the percentage of women who conceived in relation to age at onset of disease The table suggests that the later the patients acquire their disease, the rarer are pregnancies after the onset of the condition

delivery tends to become chronic (Rauramo, Kasanen, and Elfving 1960)

The effects of past kidney diseases on the course of pregnancy and delivery are less well known After nephrectomy, some patients suffer from retention of N P N and increased blood pressure, and in the past pregnancy has therefore not been recommended (Smith 1944, Dieckman 1952) Acute nephritis in childhood does not affect the course of pregnancy (Dieckman 1952) On the other hand, in a series of 15 patients with chronic nephritis, 8 had toxæmia during pregnancy (Reid *et al* 1939)

Material

The material comprises 541 women who had reached fertile age by 1960 and who had been in hospital for nephritis or pyelonephritis during 1930–1957 in the departments of medicine or pædiatrics of the Turku University Hospital or in the City Hospital for Epidemic Diseases of Turku Census records were consulted for data on their pregnancies after their kidney disease Obstetric case records were studied for all deliveries that took place in the city of Turku

No information was obtained from 30 women Thus the final material consists of 511 cases or 94 5 per cent of the original total

Of these cases, 118 were diagnosed as nephritis, 393 as pyelonephritis

Results

302 (59 1 per cent) of the 511 women had one or more deliveries These included 55 9 per cent of the nephritis group and 60 0 per cent of the pyelonephritis group The total number of deliveries was 545 An additional 14 women had histories of only spontaneous or induced abortion, so that conception had taken place in 316 women or 61 9 per cent The number of children in the different groups is given in Table I

One hundred and fifty one or exactly one-half of the 302 parous, women had their deliveries in Turku and could thus be studied through obstetric case histories

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Table IV *Effect of Duration of Disease on Fertility and Mortality*

Duration of Disease		> 2 Weeks	2–4 Weeks	1–3 Months	> 3 Months	Relapse
Nephritis	Nulliparous	9	6	14	19	10
	Deaths	0	0	3	11	3
	Parous	13	28	19	6	4
	Deaths	4	0	0	0	1
Pyelonephritis	Nulliparous	115	18	8	6	55
	Deaths	4	0	0	4	5
	Parous	208	23	2	3	66
	Deaths	1	1	0	0	1

disease the lower the incidence of conception Relapse of the primary disease clearly impairs the prognosis in all groups

Effect on Mother s Prognosis of Interval between Onset of Disease and Pregnancy

Of the 6 deaths in mothers with pregnancies after the onset of disease 5 *occurred in patients with intervals of less than 3 years between onset of disease and delivery* (Table V) In 4 cases the condition was originally classified as moderate

Significance of Complications and Clinical Findings

Blood Pressure

Of the patients with elevated systolic blood pressure during the disease 22 subsequently became pregnant Only 2 of them had elevated blood pressure during pregnancy Of the 17 women with increased diastolic blood pressure during pregnancy only one had elevated systolic blood pressure No other complications occurred

Nonprotein Nitrogen

Of the 25 women with increased nonprotein nitrogen during the illness 15 died during the observation period Only 3 became pregnant and of these one died Obviously patients of this group

Table II *Effect of Age at Onset of the Disease on the Parity and Mortality*

P = Pyelonephritis
N = Nephritis

Age at Onset of Disease	Number of Children								
	0		1		2		3		>3
	P	N	P	N	P	N	P	N	P
0–10	0	1	0	5	1	2	0	6	0
10–15	1	2	8	5	0	10	0	0	0
15–20	9 (1)[1]	12 (4)	21	7	22	1	8	0	0
20–25	43 (3)	10 (4)	28	6	29	7 (2)	16	2 (2)	11 (1)
25–30	42	10 (3)	31	3	25	6	5	1	5
> 30	52 (4)	13 (3)	17 (1)	3	9	0	0	0	0
Total	147 (8)	48 (14)	105 (1)	29	86	26 (2)	29	9 (2)	16 (1)

[1] Figures in parentheses indicate those who died during observation period

Table III *Percentage of Women Who Conceived in Relation to Age at Onset of Disease*

Age at Onset of Disease	Women who Conceived %		Deaths %	
	P	N	P	N
0–10	100	93	0	0
10–15	89	88	0	0
15–20	84	43	0	0
20–25	64	60	1	16
25–30	63	52	0	0
> 30	34	19	1	0

Effect of Duration of Disease on Fertility and Mortality

The effect of the duration of the disease on fertility and mortality is presented in Table IV Among nulliparous women the prognosis, especially of nephritic patients, deteriorates with increased duration of the disease Of those ill for more than 3 months, more than half died during the observation period On the other hand the table suggests that the duration of the disease had an obvious effect on fertility – the longer the duration of the

9 died during the observation period Severe hæmorrhages during pregnancy occurred in 9 of the parous patients Of patients with pyelonephritis, 140 had anæmia, and 89 of those later became pregnant Only one of these died The number of complicated pregnancies was, however, comparatively large Toxæmia occurred in 8, increased blood pressure in 15, and severe hæmorrhage (over 500 cc) in 4 cases Of the children, 2 died and 4 were underweight Most of the patients showed no sign of increased blood pressure or œdema during the disease proper

Urography

In 30 cases of pyelonephritis major rœntgenographic abnormalities were found Most of them were congenital, and some patients had hydronephrosis Of those not operated upon, 8 later gave birth without complications Their prognosis was not impaired by pregnancy

Toxæmia

Of the 66 nephritic parous patients, toxæmia occurred in 11 per cent, the onset in 6 per cent being before the 24th week of pregnancy In patients with previous pyelonephritis, toxæmia occurred in 11 per cent, and in 5 per cent the toxæmia was manifest before the 24th week of pregnancy

The severity of the primary condition had surprisingly little effect on the incidence of toxæmia Only one of the toxæmia patients had a history of increased blood pressure during the disease Similarly the occurrece of œdema during the kidney disease had little effect on the incidence of toxæmia Of the anæmia patients with pyelonephritis 12 per cent later had toxæmia Without exception the toxæmia occurred during the first pregnancy after renal disease

The interval between the kidney disease and the pregnancy seems to show a correlation with the incidence of toxæmia This correlation is given in Fig 1 It is shown that *if a pyelonephritic patient conceives in less than one year after her disease the incidence of toxæmia is 14 6 per cent If on the other hand, there is an interval of more than 3 years the incidence of toxæmia is*

Table V *Effect on Mother s Prognosis of Interval between Onset of Disease and Pregnancy*

Interval in Years		< 1		1–3		3–5		> 5	
		Slight	Severe	Slight	Severe	Slight	Severe	Slight	Severe
Nephritis	Number	4	0	8	3	5	5	41	5
	Deaths	0	0	3	0	0	1	0	0
Pyelo-nephritis	Number	61	14	73	13	39	1	39	5
	Deaths	0	0	1	1	0	0	0	0

should not be allowed to conceive, as their basic prognosis is very poor

Œdema

Œdema in nephritic patients was of prognostic significance Œdema occurred during the disease in 42 patients, of whom 13 died Of those who became pregnant, 25 per cent died Thus the significance of œdema associated with renal disease is greater than that of elevated blood pressure

Impaired Urinary Concentration

The first symptom of the chronic phase of pyelonephritis is impaired urinary concentration Of the 71 patients in this group, 6 died during the observation period, but the number of pregnancies had no effect on their prognosis

Excretion of Phenolsulphonphthalein

The renal function of pyelonephritic patients was investigated in hospital by excretion of phenolsulphonphthalein Pregnancy occurred subsequently in 11 of the 25 women with excretion of less than 40 per cent The mothers tolerated pregnancy well, but 3 of the children died with signs of asphyxia

Anæmia

Anæmia associated with renal disease generally indicates a chronic condition Of the 28 patients with nephritis and anæmia,

exceeding 500 cc occurred in two cases, and two Cæsarean sections were performed

Of the 128 pyelonephritic patients with full data available 29 had œdema during pregnancy and 34 showed albuminuria Both the systolic and the diastolic blood pressure increased in 29 cases Bacteriological examination of the urine was not performed unless the patient had definite symptoms, and bacilluria was therefore only demonstrated in 8 cases A history of pyelonephritis apparently does not signify a great risk of relapse of urinary infection during pregnancy, but rather of other renal complications Cæsarean section was performed in 8 instances Generally the severity of complications depended on the interval between illness and delivery During the first three years were many symptoms, whereas after three years delivery took place without complications At delivery, 7 patients had hæmorrhage exceeding 500 cc, and the only maternal death was due to hæmorrhage caused by afibrinogenæmia

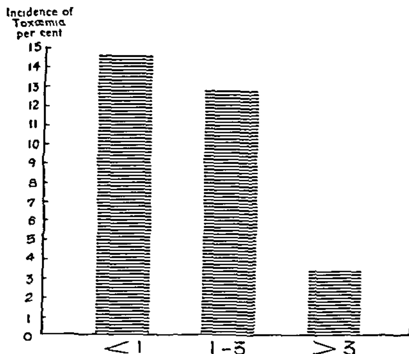
Cæsarean Section

Cæsarean section was performed on a total of 11 patients or 7 3 per cent In 7 cases, the indication was a contracted pelvis in 3 abnormal position and in one fœtal asphyxia According to Rauramo and Kivikoski, the incidence of Cæsarean sections in the Turku University Hospital in 1938–1960 was 7 0 per cent

Prognosis for Children

The perinatal mortality in the present material was 3 0 per cent Among cases in which follow up examination was possible, asphyxia at birth was found in 5 3 per cent Premature deliveries (weight of fœtus at birth less than 2 500 g) occurred in 8 per cent of the cases, and 1 3 per cent gave birth to infants with a weight of less than 1,500 g

The correlation between perinatal mortality and the interval between kidney disease and pregnancy is illustrated in Fig 2 The prognosis for the infant was poorest when birth took place less than one year after the disease In the group with disease-to-pregnancy intervals of less than one year mortality was 5 1 per



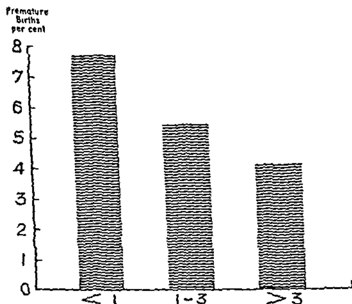
Interval between onset of kidney disease and the pregnancy in years

Fig. 1. Incidence of toxæmia and the interval between the onset of kidney disease and the pregnancy.

only 3.3 per cent. These figures are not directly comparable with the present incidences of toxæmia in our hospitals, because the case histories have a considerable time spread and the criteria for diagnosis of toxæmia have changed. Probably, several instances of slight toxæmia fail to appear in our records. The severity of the toxæmia in the present material is reflected by the high incidence (15 per cent) of induced abortions necessitated by toxæmic states.

Course of Pregnancy and Labour

Pregnancy and labour was investigated in 151 cases. Œdema and proteinuria occurred during pregnancy in only 5 of the 23 nephritic patients. At delivery, 5 had increased systolic blood pressure and 2 increased diastolic blood pressure. Hæmorrhage



Interval between onset of kidney disease and the pregnancy in years

Fig 3 Correlation between premature births and the interval between onset of kidney disease and pregnancy

groups As far as could be ascertained, 21 of the patients had been in hospital after their kidney conditions because of abortions, and 7 of them had records of later delivery None of them died

Induced Abortions

According to available information, abortions had been induced in 14 of the patients 9 of whom had also had live births after their illness During the observation period 2 of them died Thus their prognosis not differ markedly from that of the others Nor can the severity of their basic condition be regarded as greater than average The indication for the abortion was generally either pregnancy very soon after the renal disease or several relapses of the kidney condition In a few cases, renal disease was first diagnosed during pregnancy, which was therefore terminated

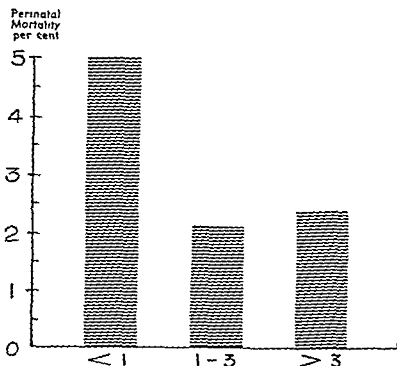


Fig. 2. The correlation between perinatal mortality and the interval between onset of kidney disease and pregnancy.

cent, in the group with intervals exceeding one year it was 2.2 per cent.

Fig. 3 gives the correlation between premature births and the disease-to-pregnancy interval. The incidence of premature births decreased with a increased interval. If the interval was less than one year, the incidence of premature births was 7.5 per cent, if the interval exceeded one year, it was 4.5 per cent. An even clearer view of the effect of recent renal disease on the prognosis for the child is obtained in *cases with records of severe kidney conditions less than one year before delivery, whose perinatal mortality rises to 14.5 per cent.*

Spontaneous Abortions

The present investigation does not yield sufficiently reliable data on spontaneous abortions to allow comparison of the different

ruption of the pregnancy may be considered during the first years especially if the patient has a history of anæmia or increased residual nitrogen during her kidney disease Examination of urine sediment and control of œdema and blood pressure are indicated during pregnancy When three years have passed since the last renal illness the prognosis remains constant

Similarly, perinatal mortality and the number of premature births are highest during the first year after renal disease

SUMMARY

The material comprises 541 women, who had reached fertile age by 1960 and who had been treated in hospital between 1930–1957 for nephritis or pyelonphritis Information was obtained in 511 cases Their obstetric case records after their kidney disease have been studied Conception occurred in 62 per cent The incidence of complications during pregnancy and labour was higher than normal The risks both for mother and fœtus increase if conception occurs during the first year after the disease whereas later pregnancies run a normal course Advice on contraception should be given and conception avoided until the critical interval of three years has passed

Acknowledgements

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Sterilization

According to available information 9 patients were sterilized One sterilization was performed in connection with a Cesarean section Of the sterilized patients, 2 died during the observation period, 3 had very severe and 6 slight kidney conditions One patient conceived later in spite of sterilization

Discussion

After renal diseases, fertility was impaired *especially in severe* cases 61 9 per cent of the total eventually became pregnant No doubt some lowering of fertility was related to the patients' common awareness of the increased risk in pregnancies after kidney conditions Adequate instruction of patients has tended to reduce the number of pregnancies and especially multiparity

The mother s prognosis was not affected adversely by pregnancy after renal disease *per se* (However, present conclusions are based merely on a 1-to 15-year observation period and not on full calculations of life expectancy) But the incidence of complications during pregnancy and labour was higher than normal The greatest *danger was that of toxaemia both before and after the 24th week* of pregnancy The mother should rest thoroughly before as well as after delivery because of proteinuria and oedema We know that kidney function is often permanently impaired by toxaemia (Rauramo, Kasanen, Castren, and Salmi 1959) Recurrent urinary tract infections also occur during pregnancy and at delivery, and they may increase the risk of chronic pyelonephritis

Clinical observations during the illness show that the toxaemia rate is highest in patients with increased nonprotein nitrogen or with anaemia, whereas oedema and increased blood pressure have no major consequences Nor does impaired concentration in pyelonephritic patients later affect the course of pregnancy

The duration of the disease decisively affects the overall prognosis *The crucial factor however is the interval between the onset of disease and conception The risk increases if conception occurs during the early years,* whereas later pregnancies run a normal course Advice on contraception should be given and conception avoided until the critical interval of three years has passed Inter

experience that the life of the fœtus is in danger, if the excretion of œstriol remains at a level of less than 10 mg/24 hrs He also points out that a sharp decrease in the excretion is a sign of fœtal death.

All these observations described have received more interest since Cassmer (1959) was able to show that a fœtal organism is of fundamental importance for the elaboration of placental œstrogens by maintaining an adequate placental circulation He concluded that the biogenetic reactions concerned with the production of progesterone are less sensitive to changes in the placental circulation

It has therefore seemed to me to be of interest to perform determinations both of pregnanediol and of œstriol on the same urine and to compare the clinical value of the two results

Procedure

During 1959–1961 we have determined the excretion of pregnanediol and œstriol in healthy pregnant women and in cases of toxæmia and tried to do the investigations on the same 24 hrs urine collections

The series consists of 22 normal pregnancies, 22 cases of pregnancy of 43 weeks or longer duration, 20 cases of mild toxæmia (albuminuria), and 29 cases of severe toxæmia (BP > 150/100 but without renal insufficiency)

For determination of œstriol a modification of Brown s method (Furuhjelm and Waller 1958) was used and pregnanediol was estimated according to Klopper (1955) All analyses were made in the routine work of our hormone laboratory the standard error of the methods being checked at regular intervals and held below 10 per cent The statistical analysis has been made according to current methods using conventional analysis of variance the figures given being mean ± standard deviation (Bonnier and Tedin 1940)

Results

The material has been divided into three different periods i e 33–38 weeks 39–42 weeks and 43–46 weeks Those cases where

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THE EXCRETION OF ŒSTRIOL AND PREGNANEDIOL IN TOXÆMIA OF PREGNANCY AND IN POSTMATURITY

BY

MIRJAM FURUHJELM

Changes of the placenta, pathological anatomical or functional, may influence its production of hormones Therefore there has been a great interest in determinations of the excretion of hormones during the last trimester of pregnancy suitable chemical methods having made such determinations possible for clinical use

Jayle and Crepy (1955) described decreased excretion of phenolsteroids in toxæmia, and Kellar *et al* (1959) found a low excretion of œstriol in eclampsia especially in cases where the infant was small Lenters (1958) in cases of severe toxæmia (BP > 160/100) described an excretion of œstriol less than 12 mg per 24 hrs, which did not increase following therapy In patients suffering from mild toxæmia the excretion of œstriol increased when the patient improved Russell *et al* (1958) stresses the clinical importance of low excretion of pregnanediol in cases of toxæmia as being an indicator of imminent fœtal death Zondek and Pfeifer (1959) have the opinion that an excretion of œstriol less than 3 mg indicates imminent fœtal death and that a value of less than 1 mg per 24 hours proves irreversible damage of the placenta and death of the fœtus If the œstriol value drops 70 per cent from the previous level they take this phenomenon as an indication of placental insufficiency Ten Berge (1960) has the

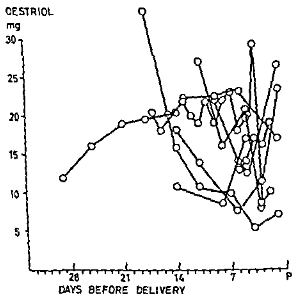


Fig 3 Excretion of œstriol in cases of mild toxæmia

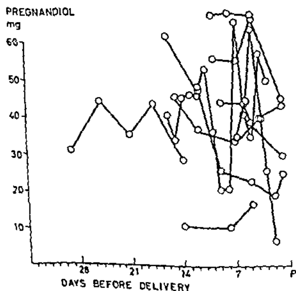


Fig 4 Excretion of pregnanediol in cases of mild toxæmia.

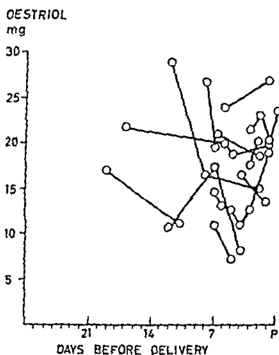


Fig 1 Excretion of œstriol in cases of normal pregnancy

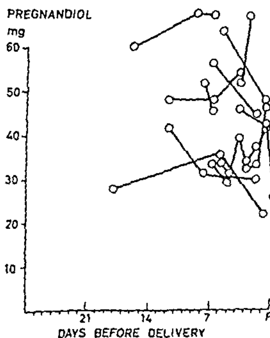


Fig 2 Excretion of pregnanediol in cases of normal pregnancy

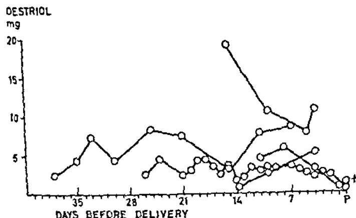


Fig 7 Excretion of œstriol in cases of severe toxæmia Placenta infarcted

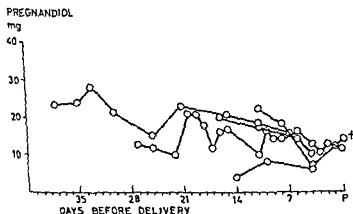


Fig 8 Excretion of pregnanediol in cases of severe toxæmia Placenta infarcted

a series of determination could be performed are illustrated separately in Figs 1–8 and the whole series is illustrated statistically in Figs 9 and 10

Normal pregnancy

Œstriol During the 33–38 weeks the mean excretion is 17 5 ± ± 5 0 mg per 24 hrs and there is no significant correlation between

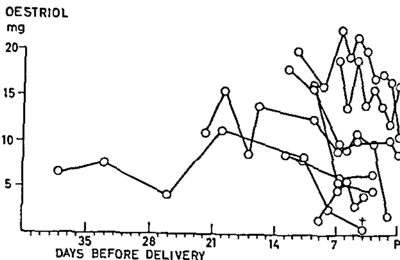


Fig 5 Excretion of œstriol in cases of severe toxæmia Placenta macroscopically normal

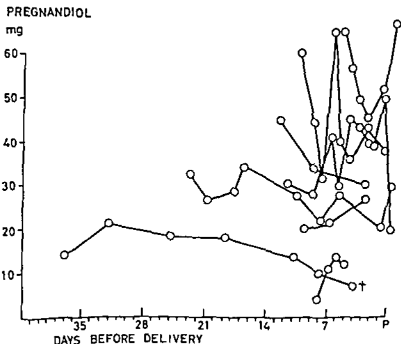


Fig 6 Excretion of pregnanediol in cases of severe toxæmia Placenta macroscopically normal

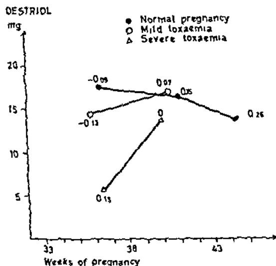


Fig 9 Excretion of œstriol Mean points (xy) and regression coefficients for the groups 33–38 weeks 39–42 weeks and 43–46 weeks of pregnancy

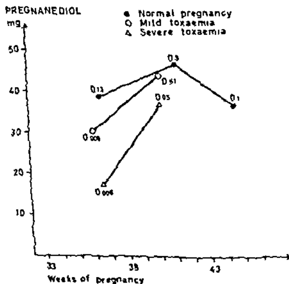


Fig 10 Excretion of pregnanediol Mean points (xy) and regression coefficients for the groups 33–38 weeks 39–42 weeks and 43–46 weeks of pregnancy

the duration of pregnancy and the amount excreted, within this period (Fig 9) In the 39–42 week group the mean excretion is 16 5 ± 5 8 mg and again there is no significant correlation between gestation period and amount excreted within these 4 weeks Fig 1 *illustrates some of the results charted in relation to delivery*

Pregnanediol During the 33–38 weeks the mean excretion of pregnanediol is 38 8 ± 15 1 mg per 24 hrs the correlation between gestation period and excretion being insignificant In the 39 42 week cases the mean excretion is 46 4 ± 19 4 mg per 24 hrs but here there is a significant ($P < 0\ 01$) negative correlation between duration of pregnancy and excretion level within the *group indicating a decrease of excretion towards delivery* Some of the individual cases are illustrated in Fig 2

During the period 33–42 weeks of pregnancy a slight decrease in the excretion of œstriol and a slight increase in the excretion of pregnanediol are evident (Figs 9 and 10)

Postmature pregnancy

In this group in which delivery occurred between the 43rd and 46th week of pregnancy, our pediatrician noted no pronounced signs of postmaturity in the babies The placenta contained an increased amount of calcifications but it seems improbable that there was pronounced placental insufficiency

Œstriol The mean excretion of œstriol is 13 9 ± 7 5 mg/24 hrs with a negative correlation coefficient time/excretion, but the value 0 10 is too small for significance A larger series might have given a significant value

Pregnanediol The mean excretion of this substance was 36 7 ± ± 12 8 mg/24 hrs without any demonstrable correlation between period of gestation and amount

Both the œstriol and pregnanediol excretion show a slight decrease during this period (Figs 9 and 10) Within this group of 22 cases there were no patients with low pregnanediol values and normal or high œstriol *values but 7 showed a pregnanediol* excretion of more than 25 mg/24 hrs and an œstriol excretion of less than 9 mg/24 hrs

without obvious infarctions and where several hormone determinations had been made are illustrated in Fig 5 (œstriol) and Fig 6 (pregnanediol) There is a more definite drop of œstriol values before the induced delivery than of the pregnanediol values In one case the obstetrician in charge of the patient did not believe the importance of the decreased œstriol excretion and the fœtus died before labour was induced

In Figs 7 and 8 the corresponding hormone excretion values of the patients with infarcted placentas are illustrated The amount of hormone excreted is lower throughout, and the importance of the dropping œstriol values is well illustrated by the fœtus that died just when the induction of labour took place in spite of the fact that the pregnanediol values were increasing

Discussion and Conclusions

From the results obtained it is obvious that the excretion of œstriol as well as the excreting of pregnanediol reflects the condition of the placenta The œstriol excretion however is a quicker indicator of the condition of the fœtus and a decrease of the œstriol excretion may be combined with an increase of the pregnanediol excretion, the fœtus being in danger in spite of this fact

For the clinician the value of a single determination is of great importance In this paper therefore the standard deviation has been printed instead of the standard error of the mean According to our present normal series an œstriol value during the 33-38 weeks period must be below 7 5 mg/24 hrs to be regarded as pathological *i e* to be below the 2 sigma limit and the corresponding value for pregnanediol is 8 6 mg/24 hrs For the period 39-42 weeks the corresponding values are for œstriol 4 9 mg/24 hrs and for pregnanediol 7 6 mg/24 hrs

The variation in this series seems to be great but depends upon the methodological errors in routine determinations with varying laboratory assistants error in the collection of urine and finally the biological variation In order to evaluate the real methodological error a sample of double determinations from the laboratory has been collected by chance covering the time period of this investigation In 50 double determinations of œstriol the standard

Mild toxæmia

Œstriol During the 33–38 weeks period the mean excretion is 14 7 ± 11 7 mg/24 hrs showing an insignificant negative correlation with time In the 39–42 weeks period the excretion is 16 9 ± ± 5 3 mg/24 hrs, the correlation coefficient with time being 0 27 indicating a probably significant (P = 0 05) increase within the period In Fig 3 demonstrating cases followed for some weeks and arranged according to time before delivery, are patients where the excretion increases during treatment, but others where a sudden drop takes place before the delivery which in these patients was induced by oxytocin drip

Pregnanediol A mean excretion of 30 ± 14 9 mg/24 hrs is observed within the period 33–38 weeks showing an insignficant correlation with time For the 39–42 weeks a mean value of 44 0 ± 16 5 mg/24 hrs is found with a probably significant (P < 0 05) positive time correlation In Fig 4 the pregnanediol excretion of the same cases as in Fig 3 is seen

The œstriol and pregnanediol values show an insignificant increase between the two periods (Figs 9 and 10) When the excretion of the individual cases of Figs 3 and 4 are compared no obvious differences are found

Severe toxæmia

Œstriol The mean excretion of œstriol during the 33rd to 38th weeks of pregnancy is 5 5 ± 4 4 mg/24 hrs with an insignificant time correlation and during the 39th to 42nd weeks 13 8 ± 4 6 mg/24 hrs (r = 0)

Pregnanediol During the 33–38 weeks period the mean excretion is 17 2 ± 7 1 mg/24 hrs without significant correlation to time, and during 39–42 weeks period 37 1 ± 13 8 mg/24 hrs with an insignificant negative time correlation

The excretion of œstriol increases highly significantly (P < 0 001) between the two periods but the increase of the pregnanediol excretion gives only a P value of 0 1 (Figs 9 and 10) A careful macroscopic examination of the placenta was made in all cases of severe toxæmia Those cases where the placenta was

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deviation was 7 4 per cent and in 50 double determinations of pregnanediol the corresponding figures was 4 6 per cent When we have got a larger normal series it will therefore be possible to elevate the lower limit for our normal variation

From the cases presented in Figs 5–8 the importance of repeated determinations is evident, and the œstriol values appear most important A sudden decrease in the œstriol excretion is a sign of danger for the fœtus On the other hand it seems that the fœtus can sometimes adapt itself to conditions associated with a rather low level of œstriol Any further decrease however is an urgent indication for delivery with as little stress as possible for the fœtus

From a practical clinical point of view only œstriol determinations seem to be necessary, an important point being a quick answer from the laboratory With the methods used in this investigation it takes 48 hrs to perform pregnanediol and œstriol determinations, but very soon there will be an œstriol method with the same accuracy which takes only one day to perform.

SUMMARY

In a series of 93 cases of pregnancy in the last trimester including examples of postmaturity and toxæmia parallel urinary determinations of œstriol and of pregnanediol were performed Both the excretion of œstriol and of pregnanediol were found to reflect the condition of the placenta, determinations of œstriol reflecting better the condition of the fœtus A sudden drop in the excretion of œstriol is serious indicating that the life of the fœtus is in danger

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THE ROUTINE ADMINISTRATION OF OXYTOCIN AND METHERGIN COMBINED IN THE THIRD STAGE OF LABOUR IN NON-INSTRUMENTAL DELIVERIES

BY

LAURI RAURAMO AND KAARLE ELFVING

Active treatment of the third stage of labour with oxytocics continues to attract interest Finnish workers who have written about the treatment of the third stage are *e g* Bjorkenheim (1937), Rauramo and Vataja (1954 and 1960) and Soiva (1954) Rauramo and Vataja (1954) reported that routine intravenous administration of oxytocin during the third stage of labour shortened the duration of the third stage and reduced the blood loss compared with the situation in parturients given routine intravenous injections of Methergin during the third stage of labour Placental retention also was somewhat less frequent in the oxytocin group than in the Methergin group In contrast, the volume of the blood lost after the third stage of labour was distinctly smaller in the Methergin than in the oxytocin group The results were clearly better in the groups receiving oxytocin and Methergin than in the control group in which oxytocics were administered only for impending hæmorrhage For routine administration during the third stage of labour oxytocin and Methergin both offer advantages and disadvantages compared with each other Therefore, the authors considered it justifiable to study whether their combined administration at the beginning of the third stage further improves the results of the active treatment of the third stage of labour

Series and Methods

The series consisted of a total of 7,596 deliveries at the Women's Clinic University of Turku As in earlier studies by Rauramo and Vataja (1954 and 1961) patients with presentation anomalies, patients delivered operatively and those who, for lack of time, were not given the drugs in question, were omitted from the series There was no maternal mortality in the series The intravenous administration of Orsturan and Syntocinon and the intravenous or intramuscular administration of Methergin produced no complications The series was divided into 4 groups

1 *The combined group consisted of 3,000 cases* As soon as the baby's head and first shoulder were born the patients of this group were given 3 VE of Orsturan (Hoechst) intravenously (2 IE of synthetic oxytocin, Syntocinon (Sandoz) was used later for some of the cases) and 0 2 mg of methylergobasine tartrate Methergin (Sandoz) intramuscularly The group originally included 3 589 successive deliveries, but 589 had to be omitted for the reasons stated The group included 994 primigravidæ and 303 parturients delivered for the fifth time or subsequent

2 *Oxytocin group* This group included 1,000 patients who were given 3 VE of Orsturan intravenously as soon as the baby's head and first shoulder were born This group originally included 1 293 successive deliveries 293 were omitted for the reasons given above The number of primigravidæ was 385 and 105 were undergoing their fifth or subsequent delivery

3 *Methylergobasine group* This group, like the oxytocin group included 1,000 patients given 0 2 mg of Methergin as soon as the baby's head and first shoulder were born A total of 1 380 case reports were examined originally in this group 380 of them were omitted for the reasons stated The group included 339 primigravidæ and 101 cases involving the fifth or subsequent parturition

4 *The control group also consisted of 1 000 cases* In this group oxytocics were given only in cases in which it was considered likely that there would be heavy bleeding For this group a total of 1 334 successive case reports were examined According to the criteria mentioned above 334 cases were eliminated The group

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THE ROUTINE ADMINISTRATION OF OXYTOCIN AND METHERGIN COMBINED IN THE THIRD STAGE OF LABOUR IN NON-INSTRUMENTAL DELIVERIES

BY

LAURI RAURAMO AND KAARLE ELFVING

Active treatment of the third stage of labour with oxytocics continues to attract interest Finnish workers who have written about the treatment of the third stage are *e g* Bjorkenheim (1937), Rauramo and Vataja (1954 and 1960) and Soiva (1954) Rauramo and Vataja (1954) reported that routine intravenous administration of oxytocin during the third stage of labour shortened the duration of the third stage and reduced the blood loss compared with the situation in parturients given routine intravenous injections of Methergin during the third stage of labour Placental retention, also, was somewhat less frequent in the oxytocin group than in the Methergin group In contrast, the volume of the blood lost after the third stage of labour was distinctly smaller in the Methergin than in the oxytocin group The results were clearly better in the groups receiving oxytocin and Methergin than in the control group in which oxytocics were administered only for impending hæmorrhage For routine administration during the third stage of labour, oxytocin and Methergin both offer advantages and disadvantages compared with each other Therefore, the authors considered it justifiable to study whether their combined administration at the beginning of the third stage further improves the results of the active treatment of the third stage of labour

λ_p	p
2 05	0 04
1 96	0 05
1 88	0 06
1 81	0 07
1 75	0 08
1 70	0 09
1 64	0 10

Results

Duration of the third stage of labour

Fig 1 shows the distribution of the cases by time In Table I, the duration of the third stage of labour in both the combined and the oxytocin group is clearly shorter than in the methylergobasine group or the control group On the other hand, no significant difference is seen in the duration of the third stage of labour between the combined and the oxytocin group The difference between the combined group and the methylergobasine group is $3\ 82 \pm 0\ 55$ min The difference is highly significant ($p < 0\ 001$)

Hæmorrhage during the third stage of labour

Fig 2 shows the cases classified by the volume of blood loss during the third stage of labour Table II shows the average blood loss per patient The volume of blood lost by patients during the third stage of labour is equally great in the combined and the oxytocin groups but distinctly smaller in both groups than in the methylergobasine group (the difference between the combined and the methylergobasine group is $13\ 6 \pm 5\ 5$ ml ($p < 0\ 02$) The volume of blood lost during the third stage of labour is clearly greater in the control group than in all the other groups

Hæmorrhage after the third stage of labour

Fig 3 shows the cases classified according to the volume of the blood lost after the third stage The volume of blood lost per patient in the different groups is shown in Table III No significant difference is displayed in the volume of blood lost after the

included 432 primigravidæ and 83 patients undergoing their fifth or subsequent parturition.

The results obtained with the control group and the methylergobasine group have been described by Rauramo and Vataja (1954) and for the oxytocin group in another work by the same authors (1961). With the exception of the oxytocics mentioned the treatment of the third stage of labour was similar in all the groups. The management of the third stage has been reviewed in detail by Rauramo and Vataja (1954).

No maternal death occurred in the whole series. No side effects from the intravenous administration of Orstiran and Syntocinon or from the intravenous or intramuscular administration of Methergin were observed.

The following formulæ were employed in the mathematical treatment of the series:

Mean $\bar{x} = \frac{1}{n} \sum_{i=1}^{k} n_i x_i$ where x_i is the centre of class i
n_i is the frequency of class i
k is the number of the classes
n is the total frequency

The standard error of the mean was calculated from the formula

$$s\{\bar{x}\} = \sqrt{\frac{[\Delta\Delta]}{n(n-1)}} \quad \text{where } [\Delta\Delta] = \sum_{i=1}^{k} n_i (x_i - \bar{x})^2$$

The standard error of the difference of two means was calculated from the formula

$$s\{\bar{x} - \bar{y}\} = \sqrt{s^2\{\bar{x}\} + s^2\{\bar{y}\}}$$

If $\frac{\bar{x} - \bar{y}}{s\{\bar{x} - \bar{y}\}} \geq \lambda_p$, the difference $(\bar{x} - \bar{y})$ shows with the risk $\leq \frac{p}{2}$ that difference of the means of the total populations of quantities x and y is > 0.

The risks of the results

λ_p	p
3.29	0.001
2.58	0.01
2.33	0.02
2.17	0.03

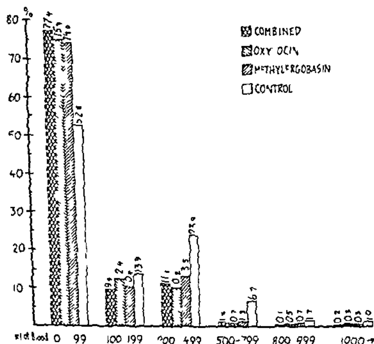


Fig 2 Extent of hæmorrhage during the third stage of labour The pillars show the number of cases in different extension groups

Table II *Hæmorrhage during the Third Stage of Labour*

Combined group	100 ± 2 4 ml
Oxytocin group	101 ± 4 5
Methylergobasin group	113 ± 4 9
Control group	200 ± 7 5

the combined than in the oxytocin group but there is no significant difference between the combined group and methylergobasine group (the difference from the oxytocin group is 23 5 ± 6 7 ml $p < 0\ 001$ and the difference from the methylergobasine group 10 2 ± 6 3 ml $p > 0\ 1$ per cent) The blood loss per patient is clearly greater in the control group than in all the other groups Table V shows the incidence of massive hæmorrhages in the different groups The criterion for massive hæmorrhage was a blood loss of 500 ml or more The table shows a greater incidence of massive hæmorrhages in the control group than in the other groups

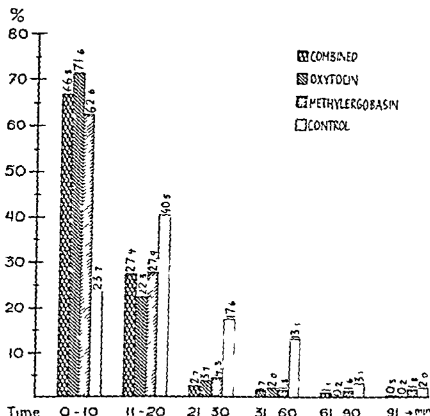


Fig. 1 Duration of the third stage of labour. The pillars illustrate the number of cases within the time groups in different series

Table I. Duration of the Third Stage

Combined group	10.38 ± 0.20 min
Oxytocin group	11.3 ± 0.28
Methylergobasin group	14.2 ± 0.51
Control group	23.5 ± 0.65

third stage of labour between the combined and the methylergobasine groups. Nor is there any significant difference between the oxytocin group and the control group. $p > 10$ per cent. The difference between the combined and the oxytocin group is 22.5 ± 4.4 ml ($p < 0.001$).

Total post-partum blood loss

Table IV shows the total blood loss after the birth of the baby in the different groups. The average loss per patient is smaller in

Table IV *Total Hæmorrhage after the Birth of the Infant*

Combined group	146 ± 3 1 ml
Oxytocin group	170 ± 5 9
Methylergobasin group	156 ± 5 5
Control group	262 ± 8 4

Table V *Massive Hæmorrhages*

(≤ 500 ml)	
Combined group	2 8 ± 0 30 %
Oxytocin group	3 0 ± 0 54 %
Methylergobasin group	2 6 ± 0 50 %
Control group	10 4 ± 0 97 %

Table VI *Retention of the Placenta*

	Combined Group	Oxytocin Group	Methylergobasin Group	Control Group
Retentio placentæ totalis	1 4 %	1 4 %	3 1 %	1 5 %
Retentio placentæ partialis	0 8 %	1 2 %	0 9 %	3 3 %
Total	2 2 ± 0 27 %	2 6 ± 0 50 %	4 0 ± 0 62 %	4 8 ± 0 68 %

the control group than in the other groups Taking the series as a whole the combined group and the oxytocin group show significantly less placental retention than the methylergobasine group and the controls The difference between the combined group and the control group is 2 6 ± 0 75 per cent $p < 0\ 001$ and the difference between the combined group and the methylergobasine group is 1 8 ± 0 67 per cent ($p < 0\ 01$) In cases of total retention of placenta the difference between the combined group and the Methergin group is 1 7 ± 0 60 per cent ($p < 0\ 01$)

Discussion

The combined administration of oxytocin intravenously and Methergin intramuscularly immediately after the birth of the baby's head and first shoulder in the management of the third

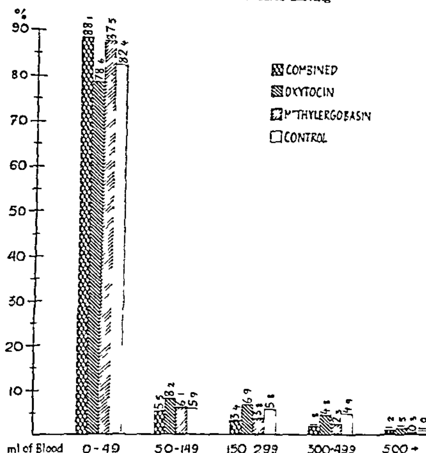


Fig 3 Extent of hæmorrhage after the third stage of labour The pillars show the number of cases in the different series in per cent within the different extension groups

Table III *Hæmorrhage after the Third Stage of Labour*

Combined group	46 ± 1 8 ml
Oxytocin group	69 ± 4.0
Methylergobasin group	43 ± 2 5
Control group	62 ± 3 6

Retained placenta

Table VI shows the incidence of retained placenta in the different groups The incidence of total placental retention is almost equal in the combined group, the oxytocin group and the control group, but about twice as great in the methylergobasine group Partial retention of the placenta is, in contrast, more common in

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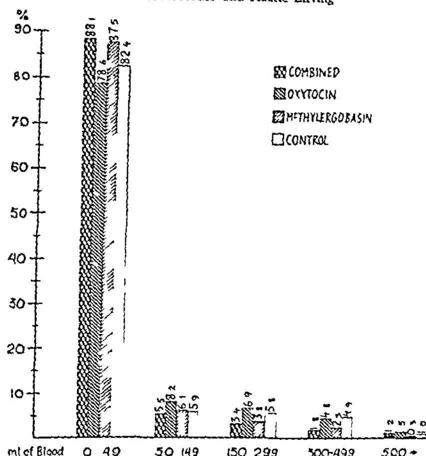


Fig 3 Extent of hæmorrhage after the third stage of labour The pillars show the number of cases in the different series in per cent within the different extension groups

Table III *Hæmorrhage after the Third Stage of Labour*

Combined group	46 ± 1.8 ml
Oxytocin group	69 ± 4.0
Methylergobasin group	43 ± 2.5
Control group	6[illegible] ± 3.6

Retained placenta

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(3 VE Orsturan, Hœchst or 2 IE Syntocinon, Sandoz) was administered intravenously and 0 2 mg of Methergin, (Sandoz) was given intramuscularly at the beginning of the third stage of labour The oxytocin group consisted of 1,000 patients who received oxytocin intravenously at the beginning of the third stage The methylergobasine group consisted of 1,000 patients who received Methergin intravenously at the beginning of the third stage The 1,000 patients of the control group were given oxytocics only when necessary As regards the duration of the third stage of labour, the combined group and the oxytocin group gave more favourable results than the methylergobasine group which, in turn was considerably better than the control group The volume of blood lost was 146 ± 3 1 ml in the combined group, 170 ± 5 9 ml in the oxytocin group, 156 ± 5 5 ml in the methylergobasine group and 262 ± 8 4 ml in the control group Massive hæmorrhages occurred in the combined, the oxytocin and the methylergobasine groups with equal frequency but in all of them considerably less often than in the control group Placental retention was less common in the combined and the oxytocin groups than in the methylergobasine group and the control group Retained placenta was commonest in the methylergobasine group

The administration of oxytocin intravenously and Methergin intramuscularly seemed to give all the benefits obtainable from the intravenous administration of either of the drugs separately and to avoid all the drawbacks observed in earlier studies of the intravenous use of oxytocin or methylergoba ine seperately

Acknowledgements

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Recieved on Jan 12th 1962

stage of labour gives all the advantages that can be achieved through the intravenous administration of either of these drugs separately The third stage is roughly as long as in the oxytocin group but shorter than in the methylergobasine group, the blood loss during the third stage is almost the same as in the oxytocin group but smaller than in the methylergobasine group, while the amount of blood lost after the third stage is practically the same as in the methylergobasine group Massive hæmorrhages are as frequent as in the oxytocin and methylergobasine groups Retention of the placenta is equally rare in the oxytocin and control groups and less common than in the methylergobasine group The total blood loss during and after the third stage of labour is as great in the combined group as in the methylergobasine group and smaller than in the oxytocin group The results are better in all three actively treated groups than in the control group Among the drawbacks of Methergin might be included the higher incidence of placental retention compared with the combined and oxytocin group A disadvantage in the oxytocin group, by contrast, was that the blood loss after the third stage was no less than in the control group *The combination of both the drugs in the manner mentioned helped to combat the tendency of Methergin to cause retention of the placenta and to reduce the tendency to more profuse post-partum hæmorrhage with oxytocin* It appears that combining intramuscular Methergin with intravenous oxytocin involves the minimum of complications and the smallest blood loss If, for economic or other reasons, only one of these two drugs is to be used, it is advisable to choose Methergin if the aim is the smallest possible blood loss, and oxytocin if the aim is the lowest incidence of retention of the placenta It is notable that all the active methods of treatment of the third stage of labour were very effective in reducing massive hæmorrhages

SUMMARY

The results of the third stage of 7,596 deliveries were compared 1,596 cases had to be eliminated because of obstetric operations or for other reasons The series was distributed into 4 groups The combined group consisted of 3,000 deliveries in which oxytocin

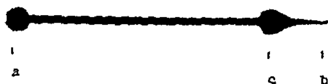


Fig 1

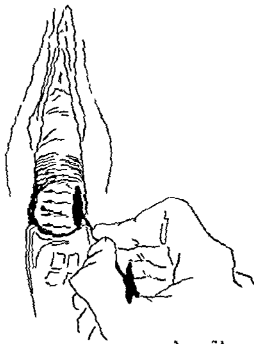


Fig 2

Thornton et al 1959, Fluhmann, 1961, Zinser, 1958, and others), and it is rather more accurate to speak about squamo columnar junction in the plural (Wespi, 1949) Those who are acquainted with colposcopy recognize such junctions as Transformation Zones The frequency of such Zones in the cervices of adult women is 70-80 per cent (Hinselmann, 1933) Reagan

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A NEW METHOD AND SPATULA FOR EXTENDED SCRAPING OF THE CERVIX UTERI[1]

BY

M SHERIF M Ch[2]

In diagnosis of early cervical carcinoma by cytological techniques a specimen taken directly from the cervix is of more value than that aspirated from the posterior fornix (Gusberg 1953, Ayre, 1947) The cervico-vaginal aspiration has the drawbacks of collecting dead rather than fresh cells (Ayre, 1947), and the cells show late stages of cellular changes in the malignant and possibly the premalignant lesions They are mixed with a considerable amount of vaginal debris and degenerated cellular material For these reasons, together with the fact that the cells are not mainly from the squamo-columnar junction, Ayre introduced the selective or surface biopsy cell scraping technique, a new and valuable concept in cancer cytology

It is true that scraping the squamo-columnar junction increases the chances for detection of preclinical carcinoma, however, the use of Ayres spatula depends on the assumption that the squamo-columnar junction lies at, beyond or within the anatomical external os The interplay between the cervical epithelia has no fixed anatomical relationship, (Kaufmann & Ober, 1959,

1 Awarded, among other articles by the author on "Diagnosis of early carcinoma of the cervix , the EDGAR–GENTILLI Prize for 1962, by the ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS

2 Lecturer, Alexandria University, Egypt U A R



Fig 1

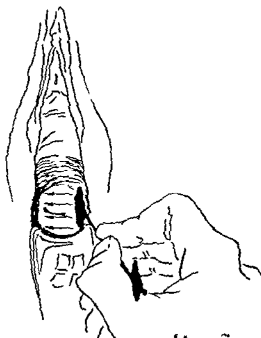


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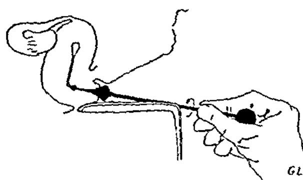


Fig 3

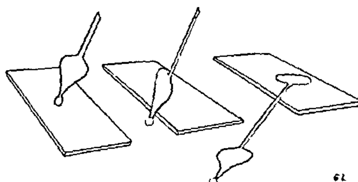


Fig 4

and Hicks (1953) and Carson (1954) by histologic studies reaffirmed the fact that carcinoma of the cervix may begin in multicentric areas Ayre's spatula by allowing circular scraping of the external os with only a narrow margin of tissues around can and must miss macroscopically undiagnosed areas of epithelial irregularities and junctions which can be a focal origin of a carcinoma The routine application of an endocervical canula in conjunction with Ayre's spatula is not only time consuming but deviates the technique from the fundamental principle of surface cell scraping Even with glandular endocervical lesions, aspiration is not specifically indicated and in spite of the rarity of such lesions, a proper scrape will not fail to demonstrate their

nature To me an ideal scraping method for the cervix uteri to detect preclinical carcinoma must include

1 Scraping of the whole vaginal surface of the cervix
2 Scraping of the external os region
3 Scraping of the endocervical canal as high up as the internal os

The spatula presented has been devised since three years and utilized to collect more than 1000 smears from cervices of different types and with different lesions All have been adequately obtained and spread, both ectocervical and endocervical

The Instrument[3]

The spatula has a length of 15 cm and a rod thickness of number four Hegar s dilator (See Fig 1) End (a) is flanged, with a maximum breadth of 70–80 mm for the flange, end (b) is knobbed the knob having the same thickness as the body The spatula has two shoulders, each with a breadth of one cm (c), situated 2 5 cm from the knob The whole instrument is constructed in wood or plastic For its use, the cervix is exposed and the flanged end is used to scrape it in straight vertical or horizontal parallel lines (Fig 2), allowing an adequate surface biopsy of the whole vaginal surface of the cervix The same rod is subsequently turned to allow the use of its knobbed end which is pushed carefully through the external os along the endocervical canal until the resistance of the internal os is felt It is then steadied and rotated in a circle of 180° (Fig 3) Both the external os region and the endocervical canal are scraped by such rotatory movement The scrape from each region is obtained over a different segment of the spatula a fact which must be kept in mind while spreading the three different smears over one or three labelled slides (Fig 4)

In target cytology under colposcopic vision the spatula proved valuable to obtain selective smears from different lesions

[3] World Distribution "KIFA Solna Sweden

SUMMARY

I A new spatula is presented, and a new method for extended scraping of the cervix uteri is described together with its principles

II The method and spatula allow the whole vaginal surface of the cervix to be scraped, together with the external os region and the endocervical canal

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THE ABO BLOOD GROUPS AND CANCER OF THE FEMALE GENITAL TRACT

BY

PER BERGSJÖ AND PER KOLSTAD [1]

Investigations into possible associations between blood groups and diseases have mainly been focused upon cancer and peptic ulcer Publications on the subject have appeared sporadically since 1920, but the early results were not statistically valid In 1953 Aird et al presented a report on 3 632 cases of cancer of the stomach from hospitals in England and Scotland The cancer patients showed a statistically significant increase in the frequency of blood group A as compared with the controls In later studies Aird et al (1954 1960) have found an increase in blood group A among patients with cancer of the pancreas and cancer of the œsophagus but a normal distribution of the ABO blood groups in cancer of the colon, cancer of the rectum, cancer of the breast bronchial cancer and pituitary adenomas The correlation between cancer of the stomach and group A has been confirmed by Segi et al (1957) in Japan, by Mosbech (1958) in Denmark, and by Beasley (1960) in Great Britain

In patients with peptic ulceration, Aird et al (1954) found a significant increase of blood group O persons The same conclusion was reached by Heisto (1956), Norway and by Beasley (1960) While other workers have been unable to find a correlation between the site of the stomach lesion and the ABO blood

[1] Research fellow of The Norwegian Cancer Society

groups, Balme and Jennings (1957) claim that patients with antrum lesions are mainly of group A and those with corpus lesions of group O, this holding true for both cancer and ulcer Sievers (1959) demonstrated an increase in plasma pepsinogen and free stomach acid in group O persons as compared with group A persons, an observation lending support to the validity of the publications here reviewed

The question of blood groups and female genital cancer was first dealt with by Johannsen in 1925 His study includes 107 *patients with cancer of the uterus from Denmark, and an increase* in group A was demonstrated, but the results were not statistically significant Significance at the one per cent level, however, was found by Segi *et al* (1957) in their study from Japan on 1,534 patients with cancer of the uterine cervix, group A predominating Hembold *et al* (1958) observed the same trend in 360 cases of cervical carcinoma in Heidelberg On summarizing data from 9 German cities and from Vienna, the same author (1959) states that women with blood group A have a 15 per cent greater probability of aquiring genital cancer than group O women This conclusion was based on studies on 7,705 persons Mosler (1958) found an increase in group A in ovarian carcinoma, whilst no difference from the control series could be demonstrated in other forms of genital cancer nor in cancer mammæ Flottorp, Hausken and Kolstad (1960) in a study on cervical carcinoma in Norway found an increase in group A among 745 patients, but no significance was claimed

Series

The present study concerns the ABO blood groups in 397 patients with cancer of the ovary and 493 patients with cancer of the uterine body For completeness we have included results extracted from the paper mentioned above by one of the authors (Kolstad) on 745 patients with cancer of the uterine cervix All the patients have been treated at The Norwegian Radium Hospital Since 1959 blood groupings have been performed on all patients on *admission Prior to that year* blood group determinations were made on surgical patients and on those who

needed blood transfusions for other reasons Thus, the data presented include 70 per cent of the patients with cancer of the uterine body and cancer of the ovary, and 57 per cent of the cancer of the uterine cervix group treated during the period of investigation

Histologically, the corpus cancer group comprises approximately 95 per cent adenocarcinomas including adenoacanthomas, and about 5 per cent sarcomas Of the ovarian tumours, slightly more than 80 per cent are adenocarcinomas and cystadenocarcinomas, the rest being undifferentiated carcinomas, granulosa or theca cell tumours and less common types About 95 per cent of the cervical carcinomas are squamous cell

Controls

The patients treated at The Norwegian Radium Hospital come from all over Norway The ABO blood group distribution varies from one part of the country to another Our cancer patients do not correspond to the geographical distribution of the population and therefore the normal blood group frequencies must be analyzed for each part of the country separately Subsequently these figures must be correlated with the geographical distribution of our patient groups to get an exact expected distribution To achieve this goal we have consulted Mourant *et al* (1958) The ABO Blood Groups where all available data on the blood group frequencies in different parts of Norway have been collected The figures on the ABO distribution thus found are based upon 21 different and non interrelated publications on presumed normal persons from 5 specified geographical regions in Norway The largest region studied is Eastern Norway The total number of observations on normal persons here is 48 258 which is the sum of 8 separate publications the blood group distribution in these being fairly homogenous The smallest region is Northern Norway where the distribution has been calculated on the basis of two studies of 1 500 and 3,425 persons respectively Four of the 21 distribution references have less than 600 single observations the smallest study being on 204 persons from Western Norway Our patients have been subdivided according to their home districts (cancer ovarii and cancer corporis uteri) or according to their birthplace(cancer cervicis uteri) The geographical distribution of the patients has been correlated with the frequency of the blood groups in the various districts and the expected distribution to be used as a reference has been calculated. As the distribution of the cervical cancer group differed slightly from the two other series the references will be seen to differ

Statistical method

The observed and expected blood group frequencies have been tested for difference from unity by the χ^2-method We feel that other methods will add little information, but of course the figures are free to be tested in any way desired

Table I *The Distribution of the ABO Blood Groups in 397 Patients with Cancer Ovarii, Compared with the Distribution in the General Population*

	A		B		AB		O	
	No	%	No	%	No	%	No	%
Observed	212	53 3	31	7 8	15	3 9	139	35 0
Expected	195	49 0	33	8 3	15	3 9	154	38 7
Difference² / Expected no	1 48		0 12		0		1.46	

$\chi^2 = 3\ 06$ 3 degrees of freedom $0\ 5 > P > 0\ 3$
No significant difference

Table II *The Distribution of the ABO Blood Groups in 493 Patients with Cancer Corporis Uteri Compared with the Distribution in the General Population*

	A		B		AB		O	
	No	%	No	%	No	%	No	%
Observed	267	54 2	41	8 3	16	3 2	169	34 3
Expected	242	49 0	41	8 3	19	3 9	191	38 7
Difference² / Expected no	2 58		0		0 47		2 53	

$\chi^2 = 5\ 58$ 3 degrees of freedom $0\ 2 > P > 0\ 1$
No significant difference

Results

The information gained is presented for each of the cancer types separately in Tables I, II and III An increase in blood group A and a corresponding decrease in group O is apparent, the trend

Table III *The Distribution of the ABO Blood Groups in 745 Patients with Cancer Cervicis Uteri, Compared with the Distribution in the General Population*

	A		B		AB		O	
	No		No	•	No		No	•
Observed	384	51 5	65	8 7	24	3 2	272	36 5
Expected	367	49.2	61	8 2	29	3 9	288	38 7
Difference² / Expected no	0 79		0 26		0 86		0 89	

$\chi^2 = 2\ 80$ 3 degrees of freedom $0\ 5 > P > 0\ 3$
No significant difference

being most marked in the cancer corporis uteri group However, none of the groups differ significantly from the normal population By putting the cancer corporis uteri and the cancer ovarii groups together, we do find a significant difference from the expected distribution on the 5 per cent level the excess of group A being a little more marked than the deficit of group O These results are presented in Table IV The blood groups B and AB are too small for a statistical evaluation

Table IV *The Distribution of the ABO Blood Groups in 890 Patients with Cancer Ovarii or Cancer Corporis Uteri Compared with the Distribution in the General Population*

	A		B		AB		O	
	No.	•	No	%	No	•	No	•
Observed	479	53 8	72	8 1	31	3 5	308	34 6
Expected	436	49 0	74	8 3	35	3 9	344	38 7
Difference² / Expected no	4 24		0 05		0 45		3 76	

$\chi^2 = 8\ 51$ 3 degrees of freedom $0\ 05 > P > 0\ 02$

The observed distribution differs significantly from that of the general population

Discussion

The fact that the cancer series of this study represents a certain percentage of the total number of the patients admitted during the period of investigation, may be a source of error There is, however, no reason to believe that the "selection" should be influenced by the blood group distribution or vice versa

The geographical distribution of the corpus cancer and ovarian cancer patients was determined according to their present address If many of them have moved from their birthplaces to other parts of the country, this may influence our calculated normal distribution Experience shows, however, that people generally move to the eastern and southern parts of the country, and these are the districts where we find the highest incidence of blood group A Hence, any alteration in our expected distribution would reduce group A and enlarge group O, thus making the trend of difference observed more marked

Combination of Tables I and II in order to demonstrate the significant difference shown in Table IV may be criticised However, cancer of the ovary and cancer of the uterine body have so many characteristics in common, that we feel justified in doing so In Table IV we have used 3 degrees of freedom as the two groups are part of the same study and were treated at the same hospital during the same period The control series were identical

Our findings point to an increase in blood group A among the cancer patients, the trend being most marked in the corpus cancer and the ovarian cancer groups The exogenous factors which play a greater part in the aetiology of cancer of the uterine cervix may conceal a similar significant trend in this group Segi *et al* (1957) found a significant increase in group A in a cancer cervicis series twice as large as ours If we continue our study, perhaps we may reach the same conclusion

The most interesting observation, however is that our results point in the same direction as all the previous reports on the same subject, namely a higher incidence of blood group A in females with genital carcinoma

Wiener (1961) argues against the statistical results of investigations such as the present one He claims that mathema-

ticians are totally ignorant of serology, whilst serologists being aware of the fallacies of the subject, avoid drawing conclusions

The factors responsible for the observed association between blood group A and cancer of the female genital tract are obscure Theories may be offered at the histopathological or at the biochemical level, or hereditary factors may be responsible Antigen A may for example influence the formation of known or unknown factors of ætiological importance, or group O blood may inhibit such factors Every effort at explanation is of course to-day purely speculative, but the information collected may be an incitement to further research

SUMMARY

The distribution of the ABO blood groups has been studied in 493 patients with cancer corporis uteri, in 397 patients with cancer ovarii and in 745 patients with cancer cervicis uteri A higher frequency of group A than expected was found in all three cancer types, but the results were not statistically significant On putting the cancer ovarii and the cancer corporis uteri cases together, significance was found on the 5 per cent level The series confirms earlier investigations on the same subject

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CARCINOMA UTERI ET OVARII

A Study from the Norwegian Radium Hospital

BY

PER BERGSJÖ

Introduction

In 1888 Reichel described the simultaneous occurrence of carcinoma ovarii and carcinoma corporis uteri in six patients In one additional case carcinoma corporis uteri was diagnosed two years after operation for ovarian carcinoma Later, several publications have stated the incidence of ovarian metastases in corpus carcinoma and vice versa Obviously to find the true incidence of cancer in both organs in one patient, parallel series of cases of primary uterine and of primary ovarian carcinoma must be examined Offut (1932) studied 520 cases of corpus carcinoma and 616 cases of ovarian carcinoma from the Mayo Clinic In 53 (4 7 per cent) she found cancer in both organs Based on histological criteria 16 were considered primary ovarian and 5 primary corpus carcinomas, while in 31 cases she was unable to determine the primary site One patient had two primary tumours Lynch and Dockerty (1945) in a similar study from the Mayo Clinic also concluded that between 4 and 6 per cent of the patients had involvement of both organs About two thirds of their 50 cases were considered primary ovarian and one third primary uterine carcinomas

In 1949 the term Cancer uteri et ovarii was suggested for the group of cases where the two tumours are not both primary

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Findings

The incidence of carcinoma corporis uteri and carcinoma ovarii in the same patient is presented in table I The over all incidence is 13 per cent

Table 1 *Carcinoma Corporis Uteri and Carcinoma Ovarii – Incidence*

	Cancer Corporis Uteri	Cancer Ovarii	Total
Cases examined	696	579	1275
Microscopic diagnosis from both organs obtained	430	454	884
Cancer in both organs	38	77	115

9 per cent of the corpus carcinomas also had ovarian carcinoma
17 per cent of the ovarian carcinomas also had corpus carcinoma
Over all incidence 13 per cent.
The incidence is related to the number of cases where the microscopic diagnosis from both organs is known

The diagnosis was established by operation in all but one of the patients with corpus carcinoma the latter being diagnosed at autopsy In the carcinoma ovarii group curettage was performed in connection with the primary operation on 353 patients (60 per cent of the total group) of whom 49 or 14 per cent also had carcinoma of the endometrium Nine of the patients with a negative curettage had cancer in the myometrium, diagnosed by operation Further operation disclosed fifteen cases and autopsy four in which curettage had not been performed

The group of 115 patients with carcinoma corporis uteri and carcinoma ovarii was analyzed further

In the majority of the cases one tumour was considered primary and the other metastatic However the determination of which was the primary and which the secondary often proved difficult Based on the pathologists reports and on the case histories the patients were grouped according to the primary site of the lesion, where a decision was possible The histological diagnoses in each of these groups are presented in table II

ones (Annual Report, 1949, p 27) It was adopted in 1950 to serve as an aid in clinical classification

Cases should be classified as Carcinoma uteri et ovarii

(1) when there is a carcinomatous involvement of both the uterus and the ovary at the first examination,

(2) when a patient previously submitted to oophorectomy because of carcinoma of the ovary and not simultaneously curetted develops a corpus carcinoma within five years after the oophorectomy,

(3) when a patient radiologically treated because of a corpus carcinoma and with a palpable pelvic tumour extrinsic to the uterus develops a carcinoma of the ovary, provided that a connection between the ovarian carcinoma and the previously noticed tumour cannot be definitely excluded at operation or post mortem

It should be observed that a classification according to paragraphs (1), (2) and (3) should be applied only when it cannot be microscopically stated that both the lesions are primary

(Quoted from the *Annual Report*, 1961, pp 10–11)

Ryden (1952) presented the material which formed the basis for the definition of the term His 106 patients with both carcinoma corporis uteri and carcinoma ovarii constituted 8 4 per cent of all corpus carcinomas, and 18 6 per cent of all ovarian carcinomas treated at the Radiumhemmet, Stockholm, from 1914 to 1943 In 50 patients the tumours were discovered coincidentally, in 25 the ovarian tumour was diagnosed first and the corpus carcinoma later, while the reverse was true of 31 cases Ryden stresses the difficulties in determining the primary site of the tumour

Material

The Norwegian Radium Hospital treats about 50 per cent of all corpus carcinomas and 25 per cent of all ovarian carcinomas discovered in Norway In the present study 696 cases registered as carcinoma corporis uteri and 579 registered as carcinoma ovarii were reviewed with regard to the incidence of cancer in both organs in the same patient These represent all the cases admitted from 1953 to 1960 inclusive *The incidence of ovarian metastases in carcinoma cervicis uteri was not reviewed*

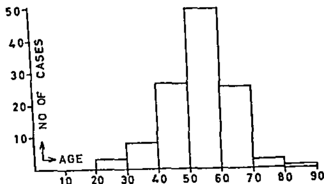


Fig 1 Age distribution – 115 patients

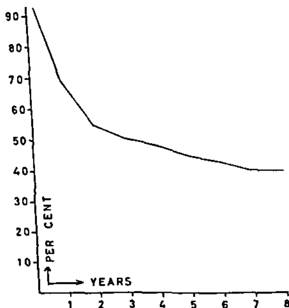


Fig. 2 Survival – 115 patients

nection with the primary treatment In the remaining twelve there was an interval of two years or more, the longest interval being eleven years Seven of these patients had their ovarian carcinoma

Table II Histological Classification

A	Primary ovarian cancer with metastases to the uterus		60 cases
	Adenocarcinoma	42 cases	
	Cystadenocarcinoma	16 »	
	Undifferentiated carcinoma	1 case	
	Granulosa cell tumour	1 »	
B	Primary uterine cancer with metastases to the ovary		21 cases
	Adenocarcinoma	19 cases	
	Sarcoma	2 »	
C	Primary site not determined		31 cases
	Adenocarcinoma	22 cases	
	Cystadenocarcinoma ovarii/ adenocarcinoma uteri	9 »	
D	Two different tumours		3 cases
	Granulosa cell tumour of the ovary/cancer corporis uteri stage 0	3 cases	

The solid adenocarcinomas are seen to dominate the list In three cases, namely the granulosa cell tumours with a carcinoma in situ of the *endometrium, there are two different cancers In five other* cases the possibility of two primary tumours was considered

In 98 patients the uterine tumour was localized to the endometrium In the remaining 17 the myometrium was involved, either by direct extension from an ovarian tumour, or by metastases The cervical mucosa was the seat of cancer in four patients

The ovarian carcinoma was unilateral in 69 and bilateral in 46 cases

The age *distribution is shown in fig 1*

The youngest patient was 24 and the oldest 80 years old Forty-five of the patients were premenopausal 61 patients had borne children, while 54 were nulliparous

The case histories reveal that 31 of the 98 patients with endometrial carcinoma had no abnormal vaginal bleeding before the primary treatment At operation for corpus carcinoma the ovaries looked normal in at least seven cases

In 103 cases carcinoma of both organs was discovered in con-

both organs Three patients had two primary tumours, in five this possibility was considered, while in the remaining 107 one tumour was primary and the other metastatic The ovaries seem to be the primary site in three fourths of the cases where a decision is possible The solid adenocarcinomas dominate the list of histological diagnoses

Points of interest regarding the case histories and the establishment of the diagnosis are reviewed and discussed

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discovered and treated first, while in five the corpus carcinoma was treated first Some of these cases may represent two primary tumours, but most are believed to be metastatic

By applying the criteria adopted for the Annual Reports, 89 of our patients can be classified as having 'carcinoma uteri et ovarii'

The survival rate is shown in Fig 2

A further study of the case histories showed that the patients who were treated primarily by radical surgery plus irradiation, and where no spread outside the uterus and the ovaries was found, had the most favourable prognosis

Discussion

While the over-all incidence of 'carcinoma uteri et ovarii" is fairly low in the Mayo Clinic series referred to, there is a striking similarity between the higher incidences reported from Sweden, and the present study from Norway If we restrict our cancer uteri cases to those with endometrial carcinoma, the reported incidence falls from 13 to 11 per cent

It seems that the ovaries are the primary seat of the tumour in three fourths of the cases in which a decision is possible At any rate, the clinical manifestations and the primary classification is 'carcinoma ovarii' in the majority of the cases

The absence of bloody discharge in one third of the patients with endometrial involvement supports the need for a curettage before laparotomy in every case of suspected ovarian malignancy In eleven of our patients a curettage revealed endometrial carcinoma succeeding bilateral oophorectomy performed in other hospitals

The case histories and the study of the survival rates suggest that the ovaries are sometimes the first and only seat of metastases in corpus carcinoma, and vice versa This stresses the importance of liberal criteria for operability, and for radical primary treatment

SUMMARY

Of 430 cases registered as carcinoma corporis uteri and 454 registered as *carcinoma ovarii, 115 (13 per cent)* had cancer in

tumours The occurrence of villi was regarded as strong pointer against a diagnosis of choriocarcinoma

Chorioadenoma destruens (invasive mole) is regarded as a hydatiform mole with excessive proliferation of the trophoblast into or through the myometrium Villi are regular findings in this condition

In syncytial endometritis different sized syncytial elements infiltrate along the tissue spaces in the endometrium and myometrium, often with a co existing inflammatory reaction

In chorioadenoma destruens and in syncytial endometritis there is but little necrosis of the myometrial tissue

Despite these apparently well defined criteria, it is not always possible to make a firm differential diagnosis as many cases do not fall strictly into any one category Moreover, different pathologists may have different opinions as to nomenclature and interpretation of the histological picture (see Brewer *et al* 1961 for example) A standardized histopathological classification according to Novak of these conditions would therefore be desirable in Scandinavia The clinical and histological data of the cases reviewed are given in Tables I and II

Preceding conditions

In only one of the 18 patients (Case 17) had symptoms of previous menstrual disorders been noted That patient had had histologically verified glandular cystic hyperplasia of the endometrium In none of the patients had the menarche occurred unusually late

In 12 possibly 13 of the cases the tumour had originated from a hydatiform mole An attempt was made to correlate the histopathologic pattern of the mole with its malignant tendency using the criteria of Hertig and Sheldon (1947) Like others (Smalbraak 1947 for example) we found this correlation unreliable and of little clinical value

Three of the 18 patients had had abortions in earlier pregnancies and one had had premature delivery in the 7th month

One patient with a chorioadenoma destruens (case 7) had also 10 years ago had a hydatiform mole which, according to Ac-

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CLINICAL AND HISTOPATHOLOGIC ANALYSIS OF A 20 YEAR SERIES OF CASES ORIGINALLY DIAGNOSED AS CHORIONEPITHELIOMA

BY

BIRGITTA NILÉHN AND MÅNS ÅKERMAN

During a period of 20 years (1941–1960) 18 patients with the diagnosis of chorionepithelioma have been treated at the Gynæcologic Department of Kung Gustaf V Jubileumsklinik, Lund On re-examination of the microscopic slides the diagnosis of *choriocarcinoma* was confirmed in only 11 cases whereas 5 were classed as *chorioadenoma destruens* (invasive mole) and 2 as *syncytial endometritis* The following analysis is mainly from a clinical point of view

Histopathologic examination

The criteria used in the histologic re-examination were those of Novak (1958) Thus, only cases with marked infiltration of the myometrium by columns or masses of trophoblastic cells Langhans' cells and syncytial elements as well as with extensive hæmorrhages and coagulation necrosis were accepted as true cases of *choriocarcinoma* (syn chorionepithelioma) Mitotic figures, hyperchromasia and cell pleomorphism were considered of less value for differentiating choriocarcinoma from benign trophoblastic proliferation, than for diagnosing malignancy in other types of

Chorioncarcinoma

Case	Age	Number of Pregnancies	Previous Abortion or Mole	Condition Antedating Trophoblastic Growth	Seat of Primary Trophoblastic Growth	Metastases	Approx. Interval between Onset and Op	Symptom Free since Op	Died within (after Op.)	Lutein Cysts	Original Diagnosis Based Mainly on
8	56	Grav —IV Para —III		Mole 5—6th m	Uterus		1 w	13 yrs		+	*Histology*
9	35	Grav —V *Para* —IV		Mole 3rd m	Uterus		1 m	7 yrs			Histology
10	33	Grav —II Para —I		Abortion *3rd* m	Uterus	Pulmones	3 m	7 yrs		–	Histology Bleeding *Pregnancy* test
11	23	Grav —IV Para —I	1 missed abortion 1 *mole*	Mole? New pregnancy?	Uterus	Vagina	1–2 w	6 5 yrs		+	Histology (vaginal metastasis)
12	37	Grav —I Para —0		Mol 3rd m	Parametrium		1 m	4 *yrs*			Pregnancy test Plasma histaminase Bleeding
13	32	Grav —V *Para* —IV	*Premature labour 7th m*	Missed abortion 7th m	Uterus	Vagina Pulmones Brain	*3 w*		2 m	?	Histology Pregnancy test Bleeding
14	[illegible]	Grav —*III* Para —II		Mole 5th m	Uterus	Pulmones Vagina	*10 m*		6 m	+	*Histology* (curettage 3 times) Bleeding
15	27	Grav —I Para —I		Normal delivery	Uterus	Behind ovary	*9 m*		5 m	+	Intraperitoneal bleeding
16	34	Grav —IV Para —III		Mole *5th m*	Pulmones		1 m		5 m	+	Pregnancy test Chest X ray Bleeding
17	24	Grav —I Para —0		Tubal pregnancy	*Tube*	Pulmones *Hepar*	3 4 m		3 m	+	Explorative *lapara*tomy
18	34	Grav —IV Para —III		Abortion *3rd m*	Uterus	Pulmones Brain (?)	4 5 m		1 m		Pregnancy test Histaminase Palpation

Table 1 *Seven Patients with Benign Trophoblastic Proliferation Treated at the Gynæcologic Department of Kung Gustaf V Jubileumsklinik, Lund, during a Period of 20 Years (1941–1960)*

	Case	Age	Number of Pregnancies	Previous Abortion or Mole	Condition Antedating Tropho-blastic Growth	Seat of Primary Tropho-blastic Growth	Metastases	Approx Interval between Onset and Op	Symptom Free since Op	Died within (after Op)	Lutein Cysts	Original Diagnosis Based Mainly on
Syncytial Endometritis	1	29	Grav —IV Para —II	1 abortion 4th m	Mole 3rd m	Uterus	Pulmones	4 m	8 yrs		?	Clinical symptoms Pregnancy test Chest X-ray *Histology* (curettage 3 times)
	2	26	Grav —I Para —0		Mole 4th m	Uterus	Pulmones	1 m	2 yrs		—	Clinical symptoms Plasma histaminase Pregnancy test Histology Chest X-ray
Chorioadenoma Destruens	3	41	Grav —II Para —I		Mole 3rd m	Uterus		3 m	19 yrs		—	Uterine bleeding, *Histology*,
	4	31	Grav —II Para —I		Mole 4—5th m	Uterus	Vagina	5 w	13 yrs		+	Histology (vaginal metastasis)
	5	36	Grav —II Para —I		Mole 4th m	Uterus		6 w	13 yrs		+	Profuse bleeding Histology Pregnancy test
	6	48	Grav —IV Para —I	2 abortions	Cervical mole 4th m	Cervix	Pelvic wall	3 m	12 yrs		+	Profuse bleeding *Palpation* Pregnancy test Histology
	7	35	Grav —V Para —III	1 mole	Mole 3rd —4th m	Uterus	Pulmones	1 m	2 yrs		+	Plasma histaminase Bleeding Chest X-ray Pregnancy test

In case 4 the patient was operated upon for a vaginal metastasis that had developed after evacuation of a mole It seems remarkable that the uterus did not show any microscopic evidence of residual trophoblast, but, according to the criteria of Wilson Hunter and Dockerty (1961), the diagnosis was chorioadenoma destruens on account of the presence of the typical metastasis in the vagina

In case 6 a chorioadenoma destruens had developed in the uterine cervix after a cervical molar pregnancy This case was published by Gorton and Sjovall (1950)

Metastatic trophoblastic growth

In benign forms of trophoblastic proliferation, secondary lesions, so called 'benign metastases are often found, mainly in the lungs but also in the vagina and in the retroperitoneal space (Smalbraak 1957, Wilson *et al* 1961) Such secondary deposits were also observed in our series

In the 2 patients with *syncytial endometritis* roentgen examination had shown suspected pulmonary lesions which disappeared soon after the operation

Of the 5 patients with *chorioadenoma destruens*, one had roentgenologically suspected pulmonary metastases one had a histologically confirmed vaginal metastasis and in one the growth had extended along the pelvic wall and had to be left at operation

Among the survivors with *choriocarcinoma*, one had had a histologically verified vaginal metastasis which had been removed at operation, and one had had roentgenologically suspected pulmonary lesions which had disappeared about one month after excision of the uterine tumour

Diagnosis

The most common symptom was uterine bleeding for which many of the patients had been repeatedly curetted A histopathological report of suspected malignancy and roentgenologically demonstrated pulmonary changes often hastened surgical intervention

Costa-Sison (1959), increases the chance of any subsequent mole becoming malignant

In one case (Case 11) it was uncertain whether the choriocarcinoma had developed from some residual fragment of the mole, possibly activated by the later pregnancy, or from the fresh pregnancy The patient expelled a mole and subsequent curettage showed no signs of malignancy One week after the curettage the *Friedman-Schneider test* became negative and after a further 3 weeks the patient had a normal period The following month menstruation did not occur and the pregnancy test was again weakly positive The plasma histaminase level, which had initially fallen, though not quite to normal level, rose again as in normal pregnancy Five months after expulsion of the mole a vaginal metastasis was detected and diagnosed histologically as a chorio carcinoma The patient was subjected to operation and radical excision of the metastasis with total hysterectomy was performed The uterus was found to contain a 15 cm long fœtus as well as a walnut-sized choriocarcinoma adjacent in the attachment of the placenta

Lepow (1959) and Novak and Seah (1954) have each described one case of choriocarcinoma during pregnancy after a hydatiform mole The interval between the expulsion of the mole and the onset of the new pregnancy was 3 years in one case and 9 months in the other

Of the remaining 10 cases of choriocarcinoma, the tumour had been antedated by a mole in 5, by early abortion in 2, by missed abortion in the 7th month of gestation in one by tubal pregnancy in one, and in one the tumour had been diagnosed 9 months after normal parturition

Localization

In 3 of the cases of *choriocarcinoma* the tumour had not in volved the uterine corpus one was situated entirely within the lung and pulmonary artery, one in the left parametrium, and the third in the right tube after tubal pregnancy Skulj (1958) was able to trace 61 cases of choriocarcinoma following tubal preg nancy in the literature, to which he added one his own

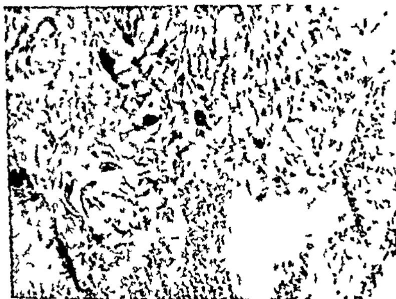


Fig 1 Case 12 Choriocarcinoma in left parametrium with hæmorrhages and moderate inflammatory reaction. Hæmatoxylin-eosin × 140

rise despite continued growth and metastasization of the tumour In case 15 in which the tumour was situated in the uterus and in which a metastatic growth behind the left ovary had to be left at operation the histaminase value persisted at a low level The histaminase curve for case 16 has been described previously by Willert (1952) In that patient the tumour which had developed after a hydatidiform mole was situated in the lungs and the pulmonary artery without any involvement of the uterus Since histaminase is believed to be elaborated mainly in the decidual cells (Swanberg 1950) this was at first taken as an explanation for the low values However curettage 6 weeks after the expulsion of the mole clearly verified the presence of uterine decidua while the operative specimen of the uterus which was removed 14 days later showed no neoplastic tissue or residual decidua

On the other hand in another non fatal case of ectopic choriocarcinoma (Case 12) in which the tumour was situated in the

A quantitative hormone analysis had been done in only a few cases and then by different methods, and will therefore not be discussed

The diagnostic and prognistic value of *pregnancy tests* such as those of Friedman-Schneider and Aschheim-Zondek was confirmed in the present study Thus, they became negative in all the survivors, but remained strongly positive in all the fatal cases examined

The large amounts of stilbestrol given in the fatal cases did not show any tendency to suppress the gonadotrophin titre sufficiently to make the pregnancy test negative

In one case of chorioadenoma destruens (Case 4) the pregnancy test was negative shortly after operation, but became positive again after a further 9 months This patient was then given stilbestrol, after which the test became and remained negative

The site of the tumour seems to have no influence on the pregnancy test but it may affect the content of plasma histaminase (see below)

In case 9 the patient was followed up for 7 months after evacuation of a mole During this period she was symptom free and the pregnancy test was negative Further tests were not performed However, after a further 5 months the patient returned because of uterine bleeding Curettage now showed choriocarcinoma and the pregnancy test was strongly positive Sixteen days after subsequent operation the test turned negative This case clearly shows the risks involved by premature termination of follow-up after a hydatiform mole

The *plasma histaminase* has been regularly checked for a varying period in 11 of the cases and occasionally in 3 A rising histaminase content was taken as supplementary evidence of residual trophoblastic tissue (Willert, 1952) The upper limit of the normal range of the plasma histaminase in non pregnant women is usually taken as 0 02γ/ml/h (test performed according to Ahlmark's technique, (Ahlmark, 1944)

However, since the histaminase content appears to be dependent on a variety of different factors, it may sometimes be difficult to interpret the value found or to reconcile it with the clinical course

Thus, in 2 of the fatal cases the histaminase content did not



Fig. 1. Case 12. Choriocarcinoma in left parametrium with hæmorrhages and moderate inflammatory reaction. Hæmatoxylin-eosin × 140

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not received postoperative radiotherapy or hormone therapy, are still alive and symptom free (survival 7 years in both cases)

The remaining 7 cases of choriocarcinoma received intravaginal radium treatment and/or roentgen irradiation of the pelvis, and in one case of the chest. One patient also received cobalt 60 teletherapy after extirpation of a vaginal metastasis In 5 of the 18 cases analysed the patients had received no radiotherapy at all

In none of the 6 fatal cases had radiotheraphy produced any demonstrable palliative or therapeutic effect, nor had heavy doses of stilbestrol, which had been given in 4 cases The 5 survivors with choriocarcinoma had not received uniform treatment, though all had been operated upon with radical removal of the tumour tissue None of these patients had received hormone therapy or chemotherapy

Discussion

The present analysis underlines the difficulties encountered in the diagnosis of trophoblastic proliferation, and particularly in the differentiation between benign and malignant cases The diagnostic tests available are often positive not only in the presence of *choriocarcinoma*, but also in cases with benign trophoblastic growth. In the benign cases metastatic growth is not uncommon As was seen in some of the present cases diagnostic curettage may sometimes be non informative or misleading

Chorioadenoma destruens may sooner or later cause acute complications such as perforation of the uterus, profuse bleeding or sepsis (Smalbraak 1957) making active intervention necessary

It thus appears that the main problem from a practical point of view, especially of young patients is to differentiate between syncytial endometritis on the one hand, and choriocarcinoma or chorioadenoma destruens on the other

This difficulty is exemplified by 2 cases of benign trophoblastic proliferation (Cases 1 and 2)

Case 1 A 29-year old woman was admitted to her local hospital because of uterine bleeding after some 10 weeks amenorrhœa A hydatiform mole was diagnosed and expelled 3 months after her last normal menstrual period.

left parametrium without involvement of the uterus (Fig 1), the plasma histaminase was increased before the operation (complete hysterectomy with bilateral salpingo-oophorectomy and radical removal of the parametrian tumour) Histologic re-examination of the operative specimen revealed only incipient' decidua in one area Nothing else abnormal was observed in the abdomen, and repeated pulmonary roentgen examinations revealed no abnormality After the operation the histaminase value returned to and remained normal

Of the remaining 4 fatal cases, 2 had been followed up with determination of the plasma histaminase Both had shown satisfactorily increased and rising values In neither of these cases had the operation been radical (Cases 17 and 18)

As expected, no difference in plasma histaminase was found between the patients with benign proliferation of the trophoblastic tissue and those with choriocarcinoma In Case 2 (see below) with a diagnosis of syncytial endometritis, the plasma histaminase level fell after the evacuation of the hydatiform mole but rose again before the operation In another patient who had chorioadenoma destruens (Case 7), the plasma histaminase behaved in the same way

Treatment and course

Of the 11 patients with choriocarcinoma 6 had died within 6 months of commencement of treatment The remaining 5 are still alive and symptomfree 4–13 years after operation, as are all those who had had a benign type of trophoblastic proliferation (follow-up 2–19 years)

All of the patients, except one, had been subjected to total or subtotal hysterectomy The adnexa had been left on one or both sides in 9 patients, 3 of whom had, however, been castrated by post-operative radiotherapy

In 4 of the patients with choriocarcinoma, one or both ovaries had been spared Two of these patients died – the operation had however, not been radical (entirely ectopic localization of the tumour in lungs and tube, respectively) The 2 others who had thus been subjected to total radical hysterectomy and who had



Fig 2 Case 2 Syncytial endometritis with different sized irregular syncytial elements interspersed in myometrium accompanied by moderate leucocytic response Hæmatoxylin-eosin. × 140

total hysterectomy at which both adnexa were left *in situ* Stilbestrol treatment was then started The histaminase value was normal about 6 weeks after the operation On examination 3 weeks after the operation the roentgenographic pulmonary findings had almost disappeared The patient is alive and symptom free 2 years after the operation

Histologic re-examination As mentioned before *it is not possible to assess* the degree of malignancy of a mole from the slides However the picture of the curettings removed on the second occasion was originally regarded as strongly suggestive of chorionepithelioma The re-examination showed extensive proliferation of the throphoblast but the abundance of villi was considered to weigh heavily against this diagnosis The operative specimen of the uterus showed myometrial infiltration of different sized syncytial elements and marked inflammatory reaction, but no typical myometrial necrosis The findings were therefore re interpreted as syncytial endometritis

In neither of these 2 cases could the condition clinically be distinguished from choriocarcinoma In Case 1 the microscopic diagnosis was uncertain but a choriocarcinoma could not be excluded and total hysterectomy was done In Case 2 the microscopic picture of the curettings was originally interpreted as choriocarcinoma

Since the uterus did not return to normal size, curettage was done on the 12th day after expulsion of the mole. Histologic examination showed necrotic parts of a hydatiform mole without definite evidence of malignancy. On further follow up the Aschheim-Zondek test was positive. Re-curettage 3 months later failed to decide whether the condition was malignant or not. Follow up was continued. The patient had had bloodstained uterine discharge ever since the expulsion of the mole.

She had felt tired and thought she had lost weight. Five months after the expulsion of the mole, the pregnancy test was still positive. Roentgen examination showed pulmonary parenchymal changes suggestive of metastases. A third curettage gave no clear evidence of choriocarcinoma which, however, could not be excluded. In view of the histologic and roentgenologic findings, the patient was then subjected to *total hysterectomy at which adnexa on* both sides were left *in situ*. The pregnancy test became negative one month after operation and remained so. Three months after operation the roentgenographic changes in the lungs were no longer demonstrable. The patient is still alive and symptom free, 8 years after the operation.

Histologic re-examination. The original histopathologic diagnosis made on the basis of the operative specimen was hydatiform mole with extensive invasion of the myometrium by chorionic tissue without any convincing signs of choriocarcinoma. On re-examination diffuse invasion of large chorionic cell elements were seen as well as villi lined with such cells but no hæmorrhages or myometrial necrosis, typical of choriocarcinoma. The amended diagnosis was syncytial endometritis.

Case 2 (fig. 2). A 26 year old woman was admitted to her local hospital because of scanty spotting in the second month of gestation. Threatened abortion was diagnosed and she was treated with progesterone and vitamin E with cessation of the bleeding. One week later, however, she was re-admitted because of pains and recurrent bleeding. The plasma histaminase level suggested a viable gestation and the patient was treated conservatively in the same way as before. In the beginning of the fourth month, however, a mole was expelled. Curettage one week later revealed no signs of malignancy. After the curettage a scanty blood stained discharge persisted. The pregnancy test was still positive one month after expulsion of the mole. Initially the plasma histaminase value decreased but too slowly. *Three weeks after* expulsion of the mole it rose again, *thereby suggesting malignant change.* Despite a slight decrease in histaminase 11 days later, *retention of trophoblastic tissue was still strongly suspected.* (Histaminase values: 17 days before expulsion of mole 1:4505, ml/h. On 11th day after expulsion 1:176, 20th day 1:7024, 32nd day 1:893, 41st day 1:1052, ml/h.) The uterus was enlarged and of unequal consistency. Curettage was repeated. On histologic examination of the curettings the condition was interpreted as *choriocarcinoma.* In addition roentgen examination showed a small pulmonary *lesion* suggestive of metastasis.

Seven weeks after the expulsion of the mole the patient was submitted to

Pedersen, Knud, Acta obst. et gynec. scandinav 41 425 1962.

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A CASE OF PRIMARY RETICULUM-CELL SARCOMA ARISING FROM THE CERVIX UTERI

BY

KNUD PEDERSEN

Very few reports are available of reticulum cell sarcomas or lymphosarcomas in the female genital tract In most of the cases described the tumour seems to have been localised in the ovaries Johnson and Soule in 1957 reported five cases of malignant lymphoma One of these seems to have been a primary lymphosarcoma arising from the cervix while the four others represented reticulum-cell sarcomatosis with secondary invasion of the uterus and the vagina The following year the same authors (Obert Soule and Johnson 1958) published a case of reticulum cell sarcoma localised in the cervix uteri Hysterectomy was performed, and at the time of publication the patient had survived for 24 years without recurrence Epperson (1950) reported a case of reticulum cell sarcoma localised in the portio mistakenly diagnosed as carcinoma and treated with radium The patient died 4 years later with signs of general sarcomatosis Stein (1949) described a case of chronic lymphatic leukæmia with leukæmic infiltration of the cervix uteri in which the first symptoms of the patient s disease were gynæcological In addition cases have been reported by Werthemann (1952) Walther (1934) and Kaiser (1953)

Novak and Andersons (1937) review of uterine sarcoma is one of the fairly comprehensive works dealing with the subject. In a series of 26 973 women examined they found 59 cases of

SUMMARY

On re-examination of 18 patients originally diagnosed as having chorionepithelioma only 11 satisfied the criteria of Novak for *choriocarcinoma* On the remaining 7, 5 were diagnosed as *chorioadenoma destruens* and 2 as *syncytial endometritis* The patients with benign trophoblastic proliferation are still alive 2–19 years after operation Five operated upon for choriocarcinoma have survived 4–13 years In the 6 fatal cases death occurred within 1–6 months of commencement of treatment

Radiotherapy showed no palliative or curative effect, in the fatal cases A standard classification of conditions with trophoblastic proliferation is desirable

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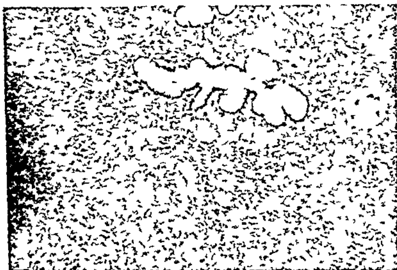


Fig 1 Sarcoma from the cervix uteri The stroma is seen to have been replaced by very closely packed cellular elements The glandular epithelium is preserved

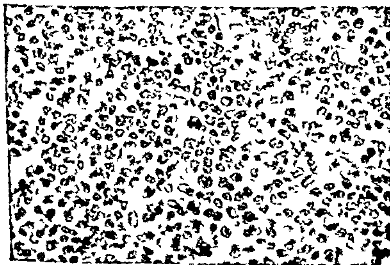


Fig 2 The tumour in higher magnification The cells are ill-defined with varying nuclear structures and a few mitoses

uterine sarcoma, among which there were no lympho- or reticulum-cell sarcomas Sugarbaker and Craver (1940) reported 1956 cases of lymphosarcoma, of which only one was of special gynæcological interest, being localised in the ovary

Case Report

A married woman aged 24, was admitted on February 25, 1961 with a polyp of the cervix uteri The patient stated that she had been in good health previously She had never been in hospital Menstruation had been regular since the age of 14, 6/28 days She had never been pregnant, and denied venereal disease

During the year prior to her admission the patient had rather frequently had a brownish occasionally bright red not particularly malodorous vaginal discharge Also during the same period she experienced occasional mild contact bleeding Her own doctor had noticed a cervical polyp as well as vaginitis The patient was therefore treated with suppositories, which had a transitory effect.

Ordinary physical examination showed no abnormalities The patient was in an average state of nutrition Hb 118 g/l E S R. 14 mm/h. Gynæcological examination revealed a 2 5 by 2 5 cm large polypous, lobulated tumour on the portio The uterus was normal in size position consistency, and mobility, and nothing of abnormal appearance was found laterally Fractional curettage was performed, as well as biopsy from the portio

Microscopy (K. Schourup) Biopsy specimens were seen to be covered on the surface by a normal cervical epithelium which continued into glandular elements, likewise of normal appearance The rest manifested itself as tumour tissue consisting of very scant stroma with scattered thin walled vessels and few collagenous fibrils as well as closely packed cellular elements, which were polygonal large, and somewhat ill-defined The nuclei differed somewhat in shape and size The majority were roundish with one or two distinct nucleoli Various mitoses were seen In some places the cytoplasm was very pale with cotton like markings while in others is was scant and rather intensely stained Tracts of lymphocyte-like cells were seen scattered between these tumour cells The whole tumour was of a solid structure and there were nowhere signs of parakeratosis or cornification The tumour seemed to be ill-defined In several places it was difficult to distinguish the tumour from the surrounding stroma because of inflammatory infiltration Reticulin staining, performed according to Wilder revealed in a few areas of the tumour a fine network of reticulin fibres Microscopy of smears from the uterine body showed the endometrium to be in the secretory phase presenting no abnormality The tumour was difficult to classify with certainty Three possibilities were considered endometrial sarcoma, lymphosarcoma and reticulum-cell sarcoma The positive reticulin findings in some

to be the therapy of choice However, Sugarbaker and Cravers (1940) report suggests a slightly better prognosis following radical surgical intervention, but their series is hardly sufficiently large to justify definite conclusions

It is also difficult to judge the prognoses for our patient, because the cases described so far are very few, and these have been treated highly individually In most cases of reticulum-cell sarcoma in the female genitals the disease has gradually developed into general sarcomatosis However, the course seen in a few cases seems to suggest that early treatment in the form of radical surgical intervention, or irradiation of a primary focus, if we can speak of such in this disease, may lead to permanent cure We may in this connection refer to the case described by Obert, Soule and Johnson (1958) of a patient who has so far survived symptom free for 24 years after radical operation The histological picture of the tumour from this patient corresponds exactly to that described and depicted in the present paper This probably justifies a certain moderate optimism

SUMMARY

A case is reported of a rarely occurring cervical sarcoma in a woman aged 24 The patient was subjected to an total hysterectomy No signs have been observed so far of local recurrence or of general disease The tumour was difficult to classify but presented the greatest resemblance to a reticulum cell sarcoma which has rarely been described at this site

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places seems to point towards the last mentioned diagnosis (See figs 1 and 2)

As it was apparently malignant tumour at the usual site of cancer of the cervix, we suggested Wertheim's operation to the patient On March 7, 1961, she was submitted to laparotomy followed by radical hysterectomy, left salpingo-oophorectomy and removal of the pelvic glands The internal genitals were found to be quite normal, with no signs of invasion by the tumour The liver was free from metastases The operation was performed in the usual manner, according to Meigs Several, up to almond size lymph nodes were removed from the pelvic floor 6 cm of the vagina was amputated together with abundant paravaginal connective tissue The upper end of the vagina was left open and peritonealised The removed uterus measured 7 by 4 5 by 3 cm A 2 5 by 2 5 cm large prominent tumour was seen on the portio It had a hæmorrhagic surface and was of a soft, friable consistency

Microscopy of the removed specimen showed tumour tissue as described above Microscopy of the removed lymph nodes showed the structure to be well preserved No atypical elements were seen a fact which, in our opinion, precluded metastases

Other examinations Hb 118–140 g/l, E S R 14–17 mm/h Red and white blood counts normal X ray of the thorax and urography before and after the operation revealed no abnormality

The postoperative course was uncomplicated The patient was fit when discharged 14 days after the operation

At out patient follow up examinations her condition was satisfactory She has had no menopausal symptoms and there has been no recurrence of tumour The blood tests performed gave normal values, with no signs of leukæmia

Comments

There is hardly any doubt that the case reported above corresponds exactly to those mentioned in the introduction, described as cases of *reticulum-cell sarcoma*, the tumour bearing a close resemblance to these with regard to histological structure The fact that the proper endometrium was quite normal militates against a diagnosis of *endometrial stroma sarcoma* The latter also differs somewhat histologically The very rare botryoid sarcoma was, of course, considered owing to the site of the tumour, but this kind of tumour has nothing in common with the one described here

It is difficult to pronounce on the best treatment of this disease, because no collected series of cases is available This tumour form being extremely radiosensitive, radiation treatment seems

Table I. *Twenty six Cases of Urinary Incontinence of 2nd and 3rd Degree Operated with Gœbell-Frangenheim-Stœckel Technique and Lengthening of Fascial Strip from Rectus Muscle*

Gynæcological Condition (Diagnoses) at Time of Operation		Time in Years between Operation and Follow-up	Completely Relieved	Nearly Completely Relieved	Partly Relieved
Cysto-and/or rectocele	9	2	1	2	
Retroposition and/or retroflexion	3	3	3	2	
Faulty innervation	3	4	2		2
Gynæcological operation performed earlier	8	5	3		
Operation for urinary incontinence performed earlier	4	6	3	1	1
			12	5	3
Parity IV–X paræ	11				
I–III paræ	12				
o paræ	3				

each and suture them together below the urethra, as in Aldridges (1942) modification of the sling operation The other possibility is to withdraw the too short fascial strip and suture it to the retropubic periosteum Both procedures have disadvantages If the original fascial strip is wide enough to permit its division into two firm parts there will be difficulty in suturing the fascia and a ventral hernia may result Dividing a strip of ordinary width may result in strips too scanty to give adequate support to the urethra and bladder neck If on the other hand, a short strip of ordinary width is sutured to the retropubic periosteum the movement of the supporting fascia under the urethra will be limited As a result of this, the support of the urethra will tend to be either too tight and inflexible or too loose

The following procedure, designed to obviate these difficulties has proved of value when performing a Gœbell-Frangenheim-Stœckel operation for urinary incontinence A midline incision is made and a fascial strip about 2 0 cm wide is cut in the ordinary way from the rectus sheet It is suitable to make the base somewhat wider at the insertion of the fascia If

Zilliacus Harry Acta obst. et gynec. scandinav 41 430, 196..

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A PROCEDURE FOR LENGTHENING THE FASCIAL STRIP AND THE BENEFITS OF THIS IN THE GŒBELL-FRANGENHEIM-STŒCKEL OPERATION FOR URINARY INCONTINENCE

BY

HARRY ZILLIACUS

Of the various operations for urinary incontinence in which muscle or the fascial tissue is brought to encircle the urethra, the method described by Gœbell-Frangenheim-Stœckel is one of the commonest In this operation a strip of fascia is cut from the midline of the rectus sheath After a midline incision has been made through the vaginal mucosa and the flaps dissected laterally, retropubic tunnels on either side of the urethra are prepared The strip of fascia is then drawn down through one retropubic tunnel and up through the other tunnel, thus encircling the urethra Sunde's (1943) modification of the sling-operation is called annuloplasty The preparation of a tunnel encircling the urethra can, according to Sjövall, (1946) be achieved without making a vaginal incision by infiltrating the periurethral tissue with saline solution This causes the vaginal mucosa to separate from the periurethral tissue The strip is then sutured to the fascia of the rectus It frequently happens, however, that the strip of fascia prepared from the rectus sheath proves to be too short Two procedures are then possible One of these is to divide the strip of fascia in two parts, draw these narrow strips down in one tunnel

one then makes a transverse incision at the base of the strip to half its width and then changes the direction of the incision through ninety degrees, cutting along the midline to a point one cm from the free end of the strip, one obtains a fascial strip of considerable strength and length When this long strip is brought back from encircling the urethra it can easily be sutured with 3-4 sutures along both sides of the rectus fascia The defect in the rectus fascia is thus filled to about one third one half of its length The suturing of the strip to the rectus fascia on both sides gurantees a flexible support for the urethra In fact, the patient frequently learns to control micturition by using the ab dominal muscles In order to avoid infection and fistulaformation especially if the tunnels have been made with the help of a vagi nal incision, the use of chromic catgut No 1-2 is preferable to silk or mersilk

With this technique, 26 cases of urinary incontinence of second and third degree were operated upon during the years 1954-1959 In three cases, these patients were nullipare and faulty innervation caused the incontinence Four to ten deliveries had occurred in 11 and 1-3 deliveries in 12 of the patients Cystoce le was present in 9 instances and retroposition in 3 There had been a previous gynæcological operation in 8 and a previous ope ration for incontinence in 4 instances In one case an infection caused the dehiscence of the sutures in the vaginal wall with the result that only a partial improvement of the incontinence was achieved The postoperative course was uneventful in the other cases and the incontinence was primarily cured in all these cases

A follow up was made in 1961 Twenty patients answered the questionnaire Twelve patients reported they were still defi nitely cured of the incontinence (3/6 years after operation, 3/5 2/4, 3/3 and 1/1)

From the answers of five patients they were classified as nearly cured (1/6 2/3 2/2 years after operation)

Three patients reported partial improvement (2/4 1/6 years after operation)

In no case had a ventral hernia developed

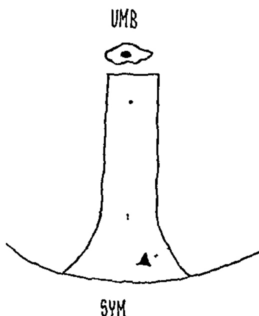


Fig 1 Dotted line indicates lengthening incision of the fascial strip cut from rectus fascia.

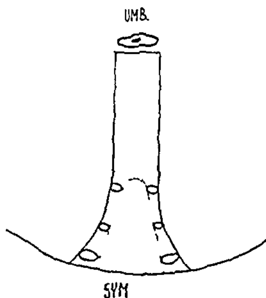


Fig 2 The fascial strip, when brought back and sutured to both sides of the rectus fascia after encircling the urethra fills up one-third of the defect in the rectus fascia

one then makes a transverse incision at the base of the strip to half its width and then changes the direction of the incision through ninety degrees, cutting along the midline to a point one cm from the free end of the strip, one obtains a fascial strip of considerable strength and length When this long strip is brought back from encircling the urethra, it can easily be sutured with 3-4 sutures along both sides of the rectus fascia The defect in the rectus fascia is thus filled to about one third one half of its length The suturing of the strip to the rectus fascia on both sides gurantees a flexible support for the urethra In fact, the patient frequently learns to control micturition by using the abdominal muscles In order to avoid infection and fistulaformation, especially if the tunnels have been made with the help of a vaginal incision, the use of chromic catgut No 1-2 is preferable to silk or mersilk

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Three patients reported partial improvement ($^2/_4$ $^1/_6$ years after operation)

In no case had a ventral hernia developed

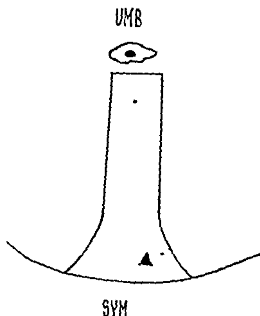


Fig 1 Dotted line indicates lengthening incision of the fascial strip cut fr rectus fascia.

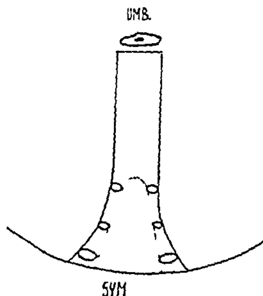


Fig 2 The fascial strip, when brought back and sutured to both sides of the rectus fascia after encircling the urethra fills up one-third of the defect in the rectus fascia

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RUPTURED LUMBAR DISCS CAUSING DIAGNOSTIC DIFFICULTIES IN ABDOMINAL OR ANOGENITAL PAIN

BY

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Introduction

Lumbar intervertebral disc protrusion may cause pain in the abdominal (Malmros 1942, Motley, 1948, Lindemann and Kuhlendahl, 1953 Hanraets 1959) or the anogenital region (Malmros, 1942, Thiele, 1950, Rose, 1954) This has been confirmed by injection of contrast medium into the disc so called discography (Lindblom, 1951, Hult, 1951 Friedman and Goldner, 1955 Fernstrom, 1957 a c, 1960)

Discographic studies (Cloward, 1959 Fernstrom, 1960) have shown as follows with respect to disc degeneration Macroscopically, degeneration will appear as a rupture in the annular ligament Two types of ruptures can then be distinguished These are ruptures with root compression the so-called herniated disc, and ruptures lacking root compression the so-called simple ruptured disc It is common to these two types of rupture that they may be the cause of incapacitating pain The pain in this instance arises in the nerve root (so called neurogenic pain) and in the disc (so-called discogenic pain) The discogenic pain is conveyed via the sinu vertebral nerve (Cloward 1959, Fernstrom, 1960, Fernstrom and Goldie 1960) and is interpreted as deep somatic pain (Fernstrom, 1960) Deep somatic pain spreads to

SUMMARY

A technical procedure is described for lengthening the fascial strip when performing the Gœbell–Frangenheim–Stœckel operation for urinary incontinence The advantages of this procedure are pointed out and the favourable results obtained in 26 cases are reported

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tion of 19–56 years and 17–65 years, respectively All the patients were examined because of pain localized in the abdomen or the anogenital region and in 61 cases there was also low back pain and/or sciatica It was characteristic of all the patients that the pain as reported in the past history could be stimulated by lumbar discography or by mechanical stimulation of the lumbar nerve root and/or the disc No less than 97 ruptured lumbar discs showing symptoms were then found This was due to the fact that in 14 cases there were multiple ruptured discs giving symptoms The distribution of level of the ruptured discs is given in Table IV, and 69 (71 per cent) were localized to the disc levels L4 and L5

Because of low back pain and/or sciatica 24 of the cases were treated by dorsal evacuation of the ruptured disc causing symp toms In 21 cases the pain either disappeared or was reduced, of these 21 the pain was localized in 18 cases to the abdomen and in three cases to the anogenital area I nine cases herniated disc was found at operation and in 15 cases simple ruptured disc

Technique

Lumbar discography was introduced by Lindblom (1948) Modified method of the author (Fernstrom 1960) is as follows A fine sized needle is inserted (without local anæsthesia) into the centre of the disc The puncture is carried out in the mide line between the spinous process The position of the needle is checked by rœntgenograms Then the contrast medium without addition of a local anæsthetic solution is injected (per discs varies between ¼ ml–5 ml) and if the ruptured disc cause symptoms, the pain de scribed in the past history will occur immediately *In contrast to* Walk (1962) I consider a rupture of disc without giving pain when injected with contrast is without any clinical significance

Mechanical stimulation of lumbar nerve root and/or disc is carried out at operation under local anæsthesia The nerve root and the disc are then explored by usual technique of operation for lumbar intervertebral disc protrusion The mechanical stimula tion is done by applying pressure to the nerve root as well as the dorsal surface of the disc and by pinching the intradiscal tissues

the sclerotome and myotome of the afferent nerve fibres involved (Kellgren, 1938) In view of the knowledge we have regarding the anatomy of the sinu-vertebral nerve (Wiberg, 1949, Pedersen, Blunck and Gardner, 1956, Stillwell, 1956) and the sclerotome of the lumbar nerve roots (Haymaker and Woodhall, 1956) and their myotome (Bing, 1945) it is quite acceptable that referred discogenic and neurogenic pain from all the lumbar disc levels can be appreciated in the abdominal or anogenital regions, a fact which was previously not acknowledged (Chapman, 1955) but which has been proved by paininducing experiments (Fernstrom, 1960) These experiments have shown that abdominal or anogenital pain in lumbar disc degeneration is most commonly a discogenic referred pain These investigations also prove that pain may be entirely discogenic and in that case will lack the symptoms and signs characteristic of root compression These cases have been published, abdominal or anogenital pain being the predominating symptom (Fernstrom, 1957 c) In these cases the genesis of the pain may be misinterpreted as being caused by visceral disease (Motley, 1948, Armstrong, 1952, Fernstrom, 1957 c) This in its turn results in unnecessary rœntgen examinations of the abdominal viscera (Hult, 1951) or laparotomy (Motley, 1948, Armstrong, 1952, Fernstrom, 1957 c)

Earlier investigations, however, do not show how often pain is misinterpreted nor to what extent it results in unnecessary rœntgen examinations of the abdominal viscera or laparotomy The factors which lead to misinterpretation of the origin of pain have not been found Furthermore, the investigations do not give any figures as to the frequency of symptoms and signs characteristic of ruptured lumbar discs in these cases, which would serve as a guide in finding the correct origin of the pain For this reason a number of cases who have all had abdominal or anogenital pain caused by ruptured lumbar discs will be described

Material

In all I have examined 78 cases during the period 1952–1960 The group includes 31 males and 47 females with an age distribu-

Table II *Operation Findings in Eleven Operations where the Origin of Pain Was Misjudged In All the Cases the Correct Origin of Pain Was a Ruptured Lumbar Disc*

Operation Findings	Number of Cases
Normal (laparotomy)	3
Polycytic ovary	2
Uterine myoma	2
Extra uterine endometriosis	1
Carcinoid of the appendix	1
Uterine peritoneal adhesions	1
Sacral root sheath fibrosis	1
Total	11

Table III *Type of Operative Procedures Performed because of Misjudged Origin of Pain In All Cases the Correct Origin of Pain Was a Ruptured Lumbar Disc*

Type of Operative Procedures	Number of Cases
Appendectomy	5
Ovarian resection	4
Subtotal hysterectomy	2
Division of adhesions	1
Radiocolysis of sacral nerve roots	1
Biopsy	1
Total	14

on ten (34 per cent) of the 29 cases Eleven operations were performed, ten laparotomies and one exploration of sacral nerve roots Table II shows the findings in the eleven operations In connection with these operations, 14 incisions were made as specified in Table III It was common to all these operations that the misinterpreted pain which led to operation remained unchanged

3 *Misinterpretation of origin of pain in relation to predominance of pain*

In the 78 cases low back pain and/or sciatica predomiated in 41 (52 per cent) In these cases abdominal or anogenital pain was

A detailed report of the above-mentioned technique has previously been published (Fernstrom, 1960)

Results

1 *Frequency and type of incorrect origin of pain*

Of 78 cases the origin of the pain was incorrectly interpreted by the doctor in 29 (37 per cent) cases The incorrect origin of abdominal or anogenital pain is given in Table I

The origin of pain was misinterpreted in five males (16 per cent) out of 31 and in 24 females (51 per cent) out of 47

Table I Type of Pain Localized Incorrectly in the Abdominal or Anogenital Region In All 29 Cases the Correct Origin of Pain Was a Ruptured Lumbar Disc

Type of Incorrect Origin of Pain	Number of Cases	
VISCERAL DISEASE		23
Ovarian cyst	5	
Cystitis	5	
Uterine tumour	4	
Appendicitis	4	
Chronic salpingitis	2	
Spastic colitis	1	
Nephrolithiasis	1	
Duodenal ulcer or cholelithiasis	1	
INCOMPLETE INGUINAL HERNIA		1
SACRAL RHIZOPATHY		1
NEUROSIS		4
Total		29

2 *Examination and operation caused by misinterpretation of the origin of pain*

Due to the origin of the pain being misinterpreted in 29 cases, roentgen examination with contrast medium was performed 24 times (82 per cent), ventricle three, bile ducts four, colon five, kidneys nine and salpinx three times, and cystoscopy four times None of these examinations revealed any pathological changes By misinterpreting the origin of the pain, operations were carried out

Table II *Operation Findings in Eleven Operations where the Origin of Pain Was Misjudged In All the Cases the Correct Origin of Pain Was a Ruptured Lumbar Disc*

Operation Findings	Number of Cases
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3 *Misinterpretation of origin of pain in relation to predominance of pain*

In the 78 cases low back pain and/or sciatica predomiated in 41 (52 per cent) In these cases abdominal or anogenital pain was

interpreted as part of lumbar rhizopathy syndrome or else these pains had been completely disregarded In the other 37 patients the abdominal or anogenital pain predominated and in 29 (78 per cent) of these the origin of pain was misinterpreted

4 Symptoms and signs in 29 cases where the origin of pain had been misinterpreted

The past history revealed low back pain and/or sciatica in 21 (72 per cent) cases There was a relation (appearing simultaneously and/or radiating from or to the same region) between these pains and the abdominal or anogenital pain in 16 (55 per cent) cases Low back pain and/or sciatica had never occurred in eight (28 per cent) cases

In 25 of the cases (86 per cent) the abdominal or anogenital pain was diffuse, aching and localized deeply (so-called visceral pain) The remaining four cases had a cutting or burning and superficial pain It was common to all 29 cases that the localiza-

Table IV *Correlation between Region of Pain and Level of Painproducing Ruptured Lumbar Disc In all the Pain was Localized in 125 Abdominal Anogenital Regions The Pain had been Verified by Discography or Mechanical Stimulation of the Nerve Root and/or the Intervertebral Disc In all 97 Disc Units (= Disc + Adjacent Nerve Roots) had been Investigated*

Regions of Pain		Level of Disc-ruptures L1	L2	L3	L4	L5	Total	
Abdominal	Hypochondriac	–	–	–	1	–	1	111
	Epigastric	–	1	–	–	–	1	
	Mesogastric							
	lateral abdominal	1	4	3	13	9	29	
	umbilical	–	4	2	7	3	16	
	Hypogastric							
	inguinal	1	3	8	23	9	44	
	pubic	2	–	2	8	8	20	
Anogenital	Pudendal	–	–	2	3	1	6	14
	Rectal	–	–	2	1	3	6	
	Coccygeal	–	–	1	–	1	2	
Total	Regions	4	12	20	55	34	125	
	Investigated discs	3	9	16	42	27	97	

tion of the pain did not correspond to the dermatome of the nerve roots which were involved in the ruptured disc showing symptoms and signs This fact also applied to the cases where the origin of pain had not been misinterpreted See Table IV

The abdominal or anogenital pain radiated in 21 cases (72 per cent) The radiation was from the lumbar region to the abdomen or anogenital area in 12 cases (41 per cent) and from the abdomen or anogenital area to the lumbar region or lower limbs in nine cases (31 per cent) In the remaining eight cases (21 per cent) the abdominal or anogenital pain was of local type

The abdominal/anogenital pain was accentuated in certain positions (bending forward, sitting, walking or lying) in 21 (72 per cent) and when coughing or sneezing in ten (34 per cent) In six of 24 females (25 per cent) where the origin of the pain had been misinterpreted, pain became more pronounced with menstruation

5 *Signs in 29 cases where the origin of the pain had been misinterpreted*

The cases were examined with respect to back signs Lasegue s sign and neurological signs Back signs are scoliosis, applanation, interspinous tenderness limited mobility and/or dorsal contracture If pain occurred, Lasegue s sign was regarded as positive Neurological signs are paresis, and reflex or sensory disturbances in the lower limb Bladder or rectal paresis was not found in any case

Positive signs occurred in 24 (82 per cent) cases, the distribution of which was as follows Back signs in 23 (79 per cent), Lasegue s sign in 13 (44 per cent) and neurological signs in sex (20 per cent) cases In three cases (10 per cent) interspinous tenderness was the only positive sign In five (18 per cent) the signs here indicated were lacking, and of these three had tenderness on palpation of the abdominal wall in the place where the pain was stated to be A completely developed root syndrome (L5 or S1) only occurred in four (13 per cent) cases

6 Special pain syndromes in cases where the origin of pain was misinterpreted

In eight cases the origin of the pain was misinterpreted due to pain syndromes which are not usually related to ruptured lumbar discs The pain syndrome could then in five cases be classified as cystalgia with urgency, described as aching pressure over the bladder with frequent desire to void In all these cases there were normal excretory pyelographic and cystoscopic findings as well as normal urine sediment This pain syndrome could be traced from the L3 disc once, the L4 disc three times, and the L5 disc once

In three cases the pain syndrome could be classified as proctalgia fugax, classified by aching or cutting pain in the rectum and a desire to defacate despite the ampulla of the rectum being empty Sigmoidoscopy and proctoscopy and X ray of the colon revealed nothing abnormal in my cases This pain syndrome originates from the L5 disc in all cases

Discussion

Abdominal or anogenital pain caused by ruptured lumbar disc may be misinterpreted as a symptom of visceral disease (Motley, 1948, Armstrong, 1952, Fernstrom, 1957 a-c) According to my case series this misinterpretation of the origin of pain occurs in 30 per cent The investigation shows also that this type of pain in ruptured lumbar discs may be interpreted as neurosis (4 per cent) or sacral rhizopathia (3 per cent) Misinterpretation of the origin of pain in ruptured lumbar disc causes, according to Hult (1951), unnecessary rœntgen examinations My investigation shows that this occurs in 82 per cent Doubt as to the origin of pain resulted in cystoscopy in several cases Pain in connection with ruptured lumbar disc may lead to laparotomy (Motley, 1948, Armstrong, 1952, Fernstrom, 1957 c) and in my series laparotomies were performed in 32 per cent when the pain was localized to the abdomen or the anogenital region According to Motley (1948) and Armstrong (1952) appendectomy and hysterectomy were performed, for instance, because of this This is in accordance with my investigations which also

show that misinterpretation of the origin of the pain may result in sacral radiocolysis

There are no discussions in the above mentioned papers as to whether there are any factors which would be contributory to an incorrect interpretation of the origin of pain My series shows that incorrect interpretation of the origin of the pain occurred more often in females (51 per cent) as compared to males (16 per cent) In all probability this depends on the position of the female intra abdominal genital organs, and also that when palpating these, benign pathological changes can be found which may be suspected as the cause of pain This phenomenon is stressed by the fact that in my series resection of cystic ovaries or hysterectomy in connection with small myomas was carried out in order to obtain relief of ruptured disc pain, the origin of which had been misinterpreted This investigation shows that the origin of pain is interpreted incorrectly only in cases where the abdominal or anogenital pain was the predominating factor But in these cases the mistake was rather common (78 per cent)

The reason for ruptured lumbar disc being misinterpreted may be that the patient is not asked to give any history as to his symptoms and signs which are typical of this disease (Motley, 1948, Chapman, 1955) My investigation shows that in fully 50 per cent of the cases a relationship between the abdominal or anogenital pain and the existing low back pain and/or sciatica has been disregarded However, it must be remembered that low back pain may also be a symptom of gynæcological disease (Vara and Waris 1952) In my series the fact that abdominal/anogenital pain becomes pronounced in certain positions of the body had also been overlooked (72 per cent), and also when coughing or sneezing (34 per cent) In view of the above it can be assumed that a more detailed past history in which the ruptured lumbar discs and their characteristic symptoms should be observed, will reduce the number of cases where of the origin of pain will be misinterpreted

According to Chapman (1955) the ruptured disc pain is a segmental neuralgia (superficial and with pain localized to the dermatome) My investigation shows that in 86 per cent the abdominal/anogenital pain in ruptured lumbar disc was of visceral

type (diffuse, aching and pain deeply localized) and in no case was the pain localized in the dermatome This must of course complicate diagnosis, as indicated by the pain having a visceral radiation (from abdomen to the back) in 41 per cent This type of pain radiation may also occur in diseases of the uterus, its adnexa or the rectum (Guerriero and Stuart, 1954) and in the prostate (Duncan, 1936) It may also be misleading that ruptured lumbar disc can give more accentuated pain during menstruation This was found in 25 per cent As far as I can see this has not been pointed out earlier

Demonstration of back signs (Hult, 1951), positive Lasegue s sign or neurological signs (Motley, 1948) in cases with diffuse abdominal/anogenital pain, seem to point to a ruptured disc Orthopædic and neurological examination in my series showed that signs typical of ruptured lumbar disc occurred in 82 per cent of the cases where the origin of pain had been misinterpreted This speaks in favour of an orthopædic and neurological examination always being carried out in diffuse abdominal/anogenital pain, in order to avoid misinterpretation of the origin of pain My investigations show that if there are no signs typical of ruptured lumbar disc the abdominal/anogenital pain can still be caused by a ruptured lumbar disc As these cases in addition may have tenderness to palpation of the abdominal wall where the pain is localized (10 per cent) the origin of pain is very difficult to trace in individual cases, even if the above-mentioned facts are known In these cases lumbar discography is useful

Pain syndromes, cystalgia with urgency and proctalgia fugax may be caused by sacral rhizopathy (Bohm Franksson and Petersen, 1956) *My investigation shows that these pain syn*dromes may also occur in ruptured lumbar discs The localization of pain may then be accepted *in view of the referred pain mech*anism which allows the pain to be localized to sclerotome or myotome (Fernstrom, 1960) On the other hand, it is not possible by referring to our knowledge of the innervation of the bladder and the rectum (White and Smithwick 1941 Bonica, 1954, Petersen and Franksson, 1955) to explain how tenesmus is provoked It cannot be denied, however, that it occurs From earlier investigations it is known that radicolysis and/or

rhizotomy in sacral rhizopathy does not always give relief (Bohm, Franksson and Petersen, 1956) My investigation shows that these cases may have ruptured lumbar discs where the origin of pain has been misinterpreted, a phenomenon which has not been acknowledged earlier

From the point of differential diagnosis I would finally point out that pain in the abdominal or anogenital region may also occur in connection with other changes either in the spinal column as thoracic ruptured discs (Tovi and Strang, 1960), spondyloarthritis deformans (Kahlmeter, 1918, Grill, 1951 a b, 1952, 1955), pelvospondylitis ossificans (Romanus and Yden, 1955, Romanus, 1957) tuberculous spondylitis (Motley, 1948) and vertebral fracture (Östling 1942, Fernstrom 1957 c), or in the spinal cord, nerve roots or arachnoidea, such as herpes zoster, tabes meningitis and tumours (Motley, 1948)

SUMMARY

Lumbar discography or mechanical stimulation of the lumbar nerve root or disc in 78 cases with ruptured lumbar discs showed as follows

Ruptured lumbar discs may cause pain in the abdominal/anogenital region Due to this localization, the cause of pain may be misinterpreted and its origin may be regarded as visceral disease, neurosis or sacral rhizopathy This misinterpretation of the origin may in turn cause roentgen examination with contrast medium of the intra abdominal viscera or the urogenital organs cystoscopy and laparotomy with appendectomy and hysterectomy as a result

The origin of the pain is misinterpreted mainly in females and in cases where the abdominal/anogenital pain is a predominating symptom Contributory reasons for mistaking the origin of pain may be benign pathological changes in the female intra abdominal genitalia, pronounced pain at menstruation and lack of symptoms and signs typical of ruptured lumbar discs

Ruptured lumbar disc may also cause pain syndromes such as cystalgia with urgency or proctalgia fugax and a misinterpretation of the origin of pain these cases may result in sacral radicolysis

In order to reduce the number of cases where the origin of pain

has been misinterpreted, it is recommended in cases with diffuse abdominal or anogenital pain that symptoms and signs typical of ruptured lumbar discs should be sought These are briefly as follows 1) Demonstrable relationship between abdominal/anogenital pain and possible low back pain and/or sciatica, 2) pronounced pain in certain positions of the body or when coughing or sneezing, 3) back signs such as scoliosis, applanation, interspinous tenderness, restricted mobility and dorsal contracture, 4) positive Lasegue's sign and 5) paresis, reflex or sensory disturbances in the lower limbs

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